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Contents

EDITORIAL

Insulin pump therapy, should we consider it more often?

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ABSTRACT

Erratic blood glucose control, hypoglycaemia unawareness and optimisation of glycaemic control during pregnancy are widely recognised indications for commencing diabetic patients on continuous subcutaneous insulin infusion (CSII) using an insulin pump. In patients without such a specific condition, the benefit of CSII over other forms of intensified treatment on glycaemic control and hypogly-caemic rate is generally viewed as too modest to warrant a change of regimen. However, the impact of the treatment regimen on psychosocial parameters is often undervalued, at least in randomised trials. This is unfortunate as quality of life and treatment satisfaction probably determine the patient's preferences more than metabolic parameters. To truly appreciate all potential benefits of either strategy (CSII or injection therapy), these data are urgently required. In the meantime, doctors should keep an open eye for the specific needs of the individual patient to find the best treatment available for that person.

Continuous subcutaneous insulin infusion (CSII) or insulin pump therapy is thought to be the best way to administer insulin to achieve the criteria of strict metabolic control set out by the Diabetes Control and Complications Trial (DCCT).[1] With CSII, short-acting insulin is infused sub-cutaneously at a varying rate to match with 24-hour basal insulin demand, whereas boosts of insulin can be administered before meals. Initially, CSII treatment was primarily meant for type 1 diabetic (T1DM) patients with so-called 'brittle' diabetes, but it was later found to also benefit patients with the Dawn phenomenon, gastroparesis, hypoglycaemia unawareness, or during pregnancy. The early pumps had

a number of technological imperfections (e.g. pump failure) and were so large that they were unacceptable for patients without such a specific condition. However, despite advances in the equipment, it is still not routinely offered as an equivalent alternative to multiple daily insulin injection (MDII) therapy in T1DM. Possible reasons for this include a general unfamiliarity with CSII and hesitance to utilise novel technologies on the part of diabetes care providers, psychological resistance against wearing an external device ('being hooked on continuously') and fears of loss of quality of life on the part of patients. The question arises whether it is time to reconsider our position towards CSII. This question can only be answered when it is clear what can be gained by switching to CSII in terms of improvement in glycaemic control and reduction in hypoglycaemic risk, and of quality of life and treatment satisfaction.

Since its introduction in the late 1970s, numerous studies have highlighted the advantages of CSII, yet many of these have methodological flaws, such as lack of control groups, small sample sizes, use of historical controls, and mixing of type 1 and type 2 diabetes and different age groups, which preclude firm conclusions. For example, in a retro-spective analysis of 138 Italian T1DM patients who were started on CSII, significant decreases were observed for both HbA$_{1c}$ (from 9.3 to 7.9%) and for hypoglycaemic events (from 0.31 to 0.09 per year) after a mean of seven years of treatment.[2] However, because a control group was lacking, a substantial part of the improvement in glycaemic control might have been the result of a study effect.[3] Furthermore, the insulin injection treatment that preceded the switch to CSII might not have been of optimal DCCT

quality, as it was largely unspecified. Parallel studies in the pre-DCCT era that compared CSII with conventional (i.e. nonoptimised) insulin injection therapy revealed differences in HbA_{1c} ranging from 0.5 to over 4% in favour of CSII, with similar hypoglycaemic risk.[4] Conversely, a recent meta-analysis of 12 randomised controlled trials that compared CSII with optimised injection therapy using MDII reported a modest 0.51% lower HbA_{1c} with CSII, whereas hypoglycaemic risk could not be evaluated because of lack of data.[5] The type of insulin used by the studies evaluated in this meta-analysis was regular insulin, except for one study where insulin lispro was used.[6] Although the results of the lispro study were consistent with the overall results of the meta-analysis, the type of insulin is relevant as fast-acting insulin analogues are currently considered the insulins of choice for pumps. A few randomised trials have been published since, which compare CSII with MDII using fast-acting analogues. In one study using insulin aspart, De Vries *et al.* reported that CSII was more efficacious than MDII in improving glycaemic control (mean HbA_{1c} 0.84% lower with CSII) in poorly controlled T1DM patients, although the number of mild hypoglycaemic events was also higher with CSII.[7] Two other studies using insulin lispro, one in 27 adults, the other in 23 children with type 1 diabetes, reported similar reductions in HbA_{1c} values and a similar rate of hypoglycaemic events with either treatment,[8,9] despite the fact that insulin lispro was not used in the MDII protocol of the latter study. A recently presented paper reported that an MDII regimen consisting of lispro insulin in combination with the long-acting insulin analogue glargine was as good as CSII with lispro to improve glycaemic control in T1DM.[10]

Thus, based on HbA_{1c} and hypoglycaemic rate, it seems unwarranted to advocate CSII to T1DM patients without a specific condition, such as erratic blood glucose control or hypoglycaemia unawareness that failed on optimised insulin (analogue) injection therapy. However, is it fair to base our judgement regarding CSII on these two parameters alone? When a similar standpoint was recently voiced, the authors were heavily criticised by both patients (or their parents) and physicians for being so narrow-minded to only consider the metabolic data.[5] Indeed, to sincerely appreciate insulin pump therapy, we need to look beyond HbA_{1c} values. In this issue of the Journal, Hoogma and co-workers highlight the importance of quality of life and treatment satisfaction when CSII treatment is considered.[11] From a patient's perspective, these factors are probably more important than a change in HbA_{1c} to determine whether CSII is started and continued or not.[4] Longitudinal studies have shown that CSII patients who were previously unhappy with insulin injection therapy generally report increased quality of life and treatment satisfaction in parallel with reductions in HbA_{1c} and hypoglycaemic rate,[12,13]

but very few data are available from randomised trials. Unfortunately, the study by Hoogma *et al.* is not a randomised trial, but a cross-sectional comparison of quality of life and treatment satisfaction between 49 patients treated with CSII for at least one year and 79 patients treated with MDII. In the CSII group, there was a preponderance of females, patients were slightly younger, had slightly shorter disease duration, and their educational level was slightly lower than that in the MDII group. Hypoglycaemic rate was identical and the HbA_{1c} value was 0.4% lower in CSII patients, a difference that did not reach statistical significance, but no differences were observed between the two groups on any of the parameters concerning quality of life. This led the authors to conclude that CSII treatment should be encouraged more in patients not optimally controlled by MDII. Although the authors should be honoured for their efforts, having so thoroughly assessed quality of life in such a large number of patients, their conclusion is somewhat premature. A (small) decrease in HbA_{1c} is probably not enough to motivate patients to decide to use CSII. For example, in a study comparing CSII with MDII, 11 out of 40 patients (the majority of whom were on CSII before the study) preferred MDII,[6] even though CSII was associated with a 0.35% lower HbA_{1c} (similar to the 0.4% difference reported by Hoogma *et al*). It should be acknowledged that the CSII group is a highly selected group; patients who for whatever reason discontinued CSII were not included, which may have affected the outcome of the questionnaires. The groups are also too different to justify a recommendation for MDII-treated patients to switch to CSII. The main reason for CSII patients to try insulin pump therapy was being unsatisfied with injection therapy in some way. As they continued CSII, I assume at least one of the following factors improved: quality of life, treatment satisfaction, glycaemic control, or rate of hypoglycaemia. Yet, this does not mean that patients who are as satisfied with MDII as the average pump user in this study is with CSII will benefit equally from switching to CSII. In this respect it is unfortunate that the study lacks an assessment of quality of life before patients were switched to CSII. As all MDII patients used regular insulin, it may be easier and cheaper to first try fast-acting analogues to optimise metabolic control before commencing CSII.

In conclusion, the study by Hoogma *et al.* shows that quality of life is as high in a sample of insulin pump users as it is in a sample of patients on MDII, but does not measure how CSII affects this parameter. Does this mean that we should not change our attitude towards CSII? Yes and no. Yes, because it is worthwhile to await the results from studies on all-analogue treatment regimens (i.e. the combination of a fast-acting analogue before meals and a long-acting analogue before bedtime). No, because patients are

entitled to information on all treatment modalities currently available and should be offered a treatment that best corresponds to their specific needs. Following that line, patients who require more flexibility from insulin treatment than MDII can provide may benefit from CSII. In the meantime, randomised trials on CSII *vs* MDII are needed that address quality of life at least as meticulous as is presented here.

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Stopper CARDS I

De Galan. Insulin pump therapy.

EDITORIAL

Competency-based training for internal medicine

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ABSTRACT

The Central College of Medical Specialities has presented guidelines for modernisation of all postgraduate speciality training programmes. These guidelines include the definition of seven general competency fields, each of them described in more detail with four key competencies. By 2006, all postgraduate speciality training programmes will be based on these competency fields. Furthermore, by then assessment of residents will be focused on the achievement of competence, rather than only on fulfilment of length of specified rotations, numbers of clinical experiences and numbers of performed skills. The application of this competency model emphasises the fact that the education of medical doctors entails more than providing them with the required theoretical and clinical knowledge and skills.

In this issue of the Netherlands Journal of Medicine, Jacobs and colleagues describe their experiences with the objective structured clinical examination (OSCE) as an assessment of medical competence.[1] This is an extremely important issue, not only for undergraduate education but also for postgraduate speciality training. Recently, the Central College of Medical Specialities (CCMS) of the Royal Dutch Medical Association (Koninklijke Maatschappij ter Bevordering van de Geneeskunst, KNMG) presented guidelines for modernisation of all postgraduate speciality training programmes.[2] These guidelines include the definition of general competency fields for all specialities, which should help professionals to develop their training programmes. The competencies are derived from Canada's Royal College of Physicians and Surgeons' 'Canadian Medical Education Directives for Specialists' (CanMEDS)

2000 model, with adjustments to adapt them to the specific requirements of the Dutch situation.[3] These adjustments are partly derived from the 2001 Dutch Blueprint of Objectives for Undergraduate Medical Training.[4] CCMS requires all postgraduate speciality training programmes to be based on these competency fields by 2006. Further, by then assessment of residents is to be focused on achieving competence, rather than only fulfilling the length of specified rotations, numbers of clinical experiences and numbers of performed skills. Outcome will be more important than input.

The CCMS has defined seven competency fields: medical performance, communication, collaboration, knowledge and science, community performance, management and professionalism. Each field is specified in four key competencies, to provide a concrete starting point for the content of training programmes and assessment (*table 1*). Some of these key competencies need no further specification; others can be specified for different specialities. CCMS demands that all societies of medical specialities formulate objectives for their speciality within this competency framework. Naturally, the formulation of many discipline-related competencies can only be done by the individual societies. However, it would be inefficient and somewhat unclear if each society would also generate competencies that are non-discipline-specific objectives, such as in the field of communication or management. At a national level, by collaborating with each other and with their surrounding regional hospitals (Onderwijs en Opleidingsregio, OOR) the eight university medical centres can very well stimulate coherence in this process, and

Table 1

Competency fields and key competencies of specialist physicians[2]

MEDICAL PERFORMANCE

The medical specialist has adequate knowledge and skills according to the profession's current standards.

The medical specialist adequately applies the diagnostic, therapeutic and preventive possibilities of the discipline, in an evidence-based way wherever possible.

The medical specialist delivers effective and ethical patient care.

The medical specialist quickly finds necessary information and applies it adequately.

COMMUNICATION

The medical specialist establishes adequate therapeutic relationships with patients.

The medical specialist listens carefully and obtains relevant patient information effectively.

The medical specialist adequately discusses medical information with patients and their family.

The medical specialist reports adequately on patient cases in oral and written ways.

COLLABORATION

The medical specialist consults effectively with other physicians and health care providers.

The medical specialist refers adequately to other health care professionals.

The medical specialist delivers adequate collegial advice.

The medical specialist supports effective interdisciplinary collaboration and chain care.

KNOWLEDGE AND SCIENCE

The medical specialist receives medical information critically.

The medical specialist contributes to the development of professional, scientific knowledge.

The medical specialist develops and maintains a personal continuing education plan.

The medical specialist contributes to the education of students, residents, colleagues, patients and others involved in health care.

COMMUNITY PERFORMANCE

The medical specialist knows and identifies the determinants of illness.

The medical specialist contributes to the health of patients and the community.

The medical specialist acts according to relevant legislation.

The medical specialist acts adequately in case of incidents in health care.

MANAGEMENT

The medical specialist finds an adequate balance between professional patient care and personal development.

The medical specialist works effectively and efficiently in a health care organisation.

The medical specialist allocates available health care resources wisely.

The medical specialist uses information technology to optimise patient care and life-long learning.

PROFESSIONALISM

The medical specialist delivers high-quality patient care with integrity, honesty and compassion.

The medical specialist exhibits appropriate personal and interpersonal professional behaviour.

The medical specialist is conscious of the limits of his/her personal knowledge and acts within these limits.

The medical specialist practises medicine consistent with ethical standards of the profession.

also make a necessary link with undergraduate educational objectives. In several regions such initiatives have already been taken.

What are the consequences of these developments for the Netherlands Association of Internal Medicine (Nederlandsche Internisten Vereeniging, NIV)? In 2002 the NIV published the updated Internal Medicine Blueprint.[5] This Blueprint can be used as the starting point to fulfil the CCMS requirements. Naturally, the transformation of the Blueprint objectives into discipline-specific competencies will require time and commitment from the NIV members. However, the Blueprint of the NIV reflects well-considered preparatory work for the determination of qualities a resident should have gained at the end of his/her period of training. Consequently, the Blueprint can be applied as a suitable basis for the formulation of key competencies of an internist.

Borleffs, et al. Competency-based training for internal medicine.

NOVEMBER 2004, VOL. 62, NO. 10

345

But the transformation of the Blueprint objectives to the competencies model also has an important added value. When applying the new model, many general competencies, important for specialists, will become explicitly part of training programmes. Both the public and leaders in medical education increasingly recognise that not only the field of medical expertise and performance, but also the other six competency fields are essential to the success of a physician. Further, it strengthens the opinion that education of medical doctors entails more than providing them with the required theoretical and clinical knowledge and skills. In this respect, we should even consider that subjects from domains outside medicine can make an important contribution to future internists' professional performance. In various higher education training programmes in the United States, such as engineering, such subjects have proved to be a highly valued addition.[6]

With the transformation of the current training programme into a competency-based programme, it is equally important that parallel strategies will be chosen to assess these competencies. Several traditional methods of evaluation can be applied for this purpose, but also the implementation of additional methods for the testing of residents' clinical competency in new competency fields will become necessary.[3] Examples can be found from several sources.[7,8]

In conclusion, the CCMS has asked the NIV to reformulate the objectives of the training programme for internal medicine and, consequently, to develop suitable methods for the residents' assessment. This will be a time-consuming activity, but we feel that the objectives of this modernisation of postgraduate speciality training will be worth the time and effort spent and will lead to a further improvement in the training of future internists.

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What do you mean: incompetent??!

Borleffs, et al. Competency-based training for internal medicine.
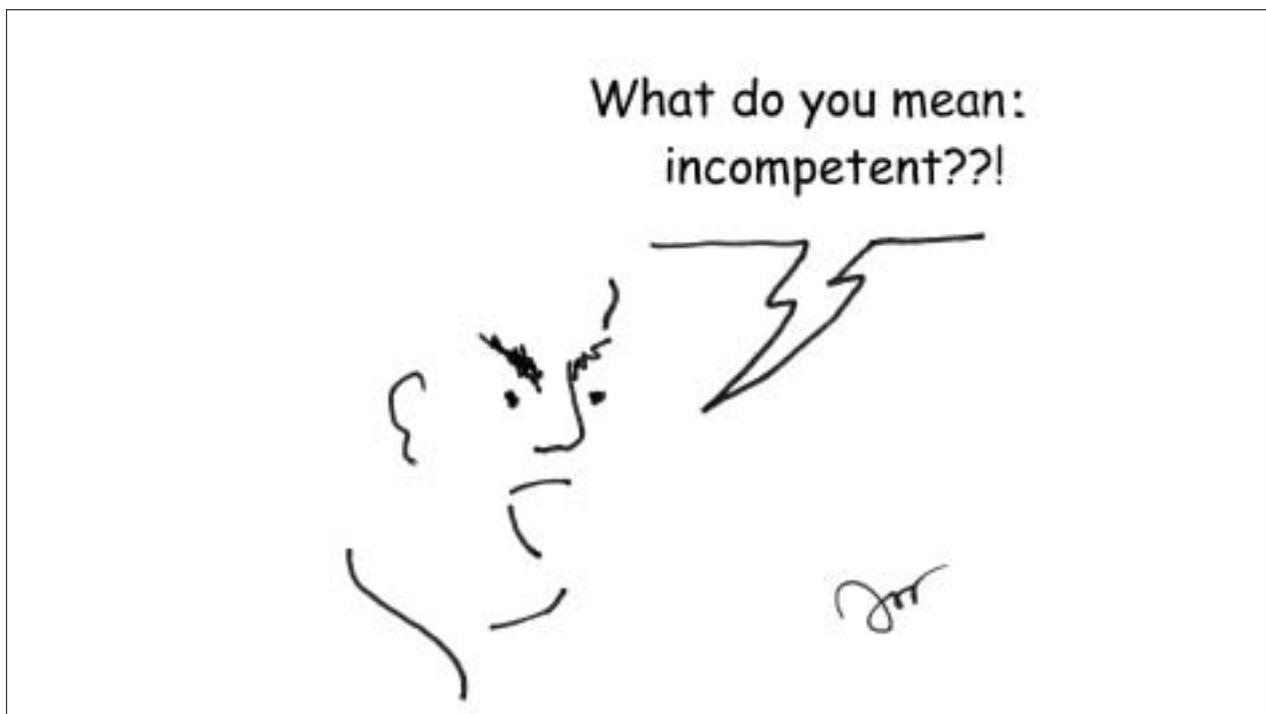
Cyclophosphamide-induced gonadal toxicity: a treatment dilemma in patients with lupus nephritis?

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ABSTRACT

For patients with lupus nephritis, a 24-month course of intravenous cyclophosphamide has been advocated as the 'golden' standard of therapy. This regimen is associated with a high risk of persistent amenorrhoea in women or azoospermia in men. The risk of infertility is thus an important issue when discussing treatment options in patients with SLE. In this article I have summarised the information on cyclophosphamide-induced gonadal toxicity. In addition a brief overview is given of the literature on treatment of lupus nephritis. The data indicate that there is no hard evidence to support the superiority of long-term i.v. cyclophosphamide. Therefore, patients with SLE and the wish to have a baby should not be primarily treated with such a regimen.

Table 1
Treatment schedule of i.v. cyclophosphamide for Lupus nephritis

INDUCTION THERAPY: MONTHS 0-6
Six monthly pulses of i.v. cyclophosphamide 750 mg/m²
Prednisolone orally 1 mg/kg/day with gradual reduction to 15 mg/day

MAINTENANCE THERAPY: MONTHS 6-24
Cyclophosphamide 750 mg/m² every 3 months +
Prednisone orally 10 mg/day

MAINTENANCE THERAPY: MONTHS 24-48
Prednisone orally 10 mg/day +
Azathioprine 2 mg/kg/day

INTRODUCTION

Lupus nephritis is a common complication in patients with systemic lupus erythematosus (SLE). If left untreated outcome is poor, most patients progressing to end-stage renal disease (ESRD) or death. Treatment with oral prednisone lacks long-term efficacy.[1] The introduction of more aggressive immunosuppressive therapy has markedly improved the prognosis in these patients.[1,2] Treatment regimens typically consist of combinations of prednisone and azathioprine, or prednisone and cyclophosphamide. In recent years the so-called 'NIH regimen' consisting of pulses of i.v. cyclophosphamide and oral prednisone has become the standard of therapy in the Netherlands. The advocated treatment schedule is given in *table 1*.
Infertility is a common complication of cyclophosphamide

therapy. Since SLE is typically a disease of young patients, issues related to fertility and reproductive ability have a prominent role in the discussion on treatment options. In the end, we must balance the risks and benefits of the various immunosuppressive regimens. For many patients, preserving fertility is worth some risk as indicated by the observations that many women with renal disease become pregnant and to a certain degree accept the associated risks, such as hypertension, premature delivery, dysmaturity and progression of renal failure.

In this commentary I will briefly address two questions:
What is the risk of infertility associated with cyclophosphamide therapy?
Is the superiority of long-term i.v. cyclophosphamide proven in controlled trials with hard endpoints?

GONADAL TOXICITY OF CYCLOPHOSPHAMIDE

Cyclophosphamide-induced amenorrhoea in women

In *table 2* an overview is given of six studies that have documented the risk of persistent amenorrhoea in patients with SLE after treatment with cyclophosphamide in cumulative dosages of 12 to 25 g.[1,3-7] The mean age of the patients was 28 years. The risk of amenorrhoea ranged from 27 to 60%. In general, amenorrhoea developed on average four months after starting cyclophosphamide therapy. Amenorrhoea may be transient, but in the studies mentioned above amenorrhoea was sustained in more than 80% of patients. These patients with sustained amenorrhoea have premature ovarian failure, and are characterised by elevated levels of gonadotropins and low levels of oestradiol. Risk factors for sustained amenorrhoea are the age of the patient at the start of therapy and the cumulative dose of cyclophosphamide. The effect of age on the incidence of sustained amenorrhoea can be appreciated from *figure 1*, which summarises the data published by Huong *et al.* and Mok *et al.*[6,8] The cumulative dose of cyclophosphamide in these studies was 12 and 18 g, respectively. In patients below 30 years of age the risk of amenorrhoea was 10%, as compared with 60% in patients above 40 years. Ioannidis calculated the risk of amenorrhoea for a standard dose of cyclophosphamide 15 g.[9] The incidence of amenorrhoea was 5 to 10% for patients <25 years, 30% for patients aged 25 to 31 years and 90% for patients >32 years. The risks of amenorrhoea are considerably less (and virtually negligible for young women) if the cumulative dose of cyclophosphamide is lower than 10 g. Mok *et al.* found no association between the route of administration and the risk of amenorrhoea.[8]

Cyclophosphamide-induced azoospermia in men

The incidence of SLE in male patients is low. Therefore, data on gonadal toxicity of cyclophosphamide in male SLE patients are lacking. Meaningful data can be derived from studies in patients who received courses of oral cyclophosphamide for idiopathic nephrotic syndrome or in patients with malignancies treated with cyclophosphamide. Several authors have evaluated the sperm count in men who had been treated in childhood or puberty due to idiopathic nephrotic syndrome.[10-14] Overall there was a clear relation between the duration of cyclophosphamide treatment or the cumulative dose of cyclophosphamide and the risk of azoospermia. *Figure 2* illustrates the reported findings. As the figure shows, the risk of azoospermia is particularly evident at cumulative dosages above 300 mg/kg, although even higher doses have been tolerated without a problem. One must realise that most patients involved in these studies were treated before puberty. Although the issue has not been settled, treatment started before onset of puberty may entail less risk of azoospermia.[15] Thus, the data may not be fully applicable to adult patients treated with cyclophosphamide. Based on the data provided, a cumulative dose of 168 mg/kg (equivalent to 12 weeks treatment at a dose of 2 mg/kg, or 12 g in total for a patient of 70 kg) is considered safe for adult patients. The latter conclusion is supported by data obtained in patients treated with i.v.

Figure 1
Risk of amenorrhoea in relation to age

Summary of data reported by Huong *et al.* and Mok *et al.*[6,8]
Cumulative dose of cyclophosphamide was 12 and 18 g, respectively. The
numbers in the bars indicate the total number of patients per age group
included in the studies.

Table 2
Amenorrhoea after cyclophosphamide therapy

AUTHOR (REFERENCE)	PATIENTS (N)	AGE (YEARS)	DOSE OF CYCLOPHOSPHAMIDE	AMENORRHOEA (N/%)
Boumpas[3]	13	28	14 pulses of 0.5-1.0 g/m²	5 (38%)
Austin[1]	20	27	16 pulses of 750 mg/m²	9 (45%)
Illei[4]	20	28	14 pulses of 1 g/m²	12 (60%)
Illie[5]	23	28	14 pulses of 1 g/m²	12 (54%)
Huong[6]	84	29	3 pulses of 0.9 g	23 (27%)
Mok[7]	55	31	20 g	24 (43%)

Ages are average values.
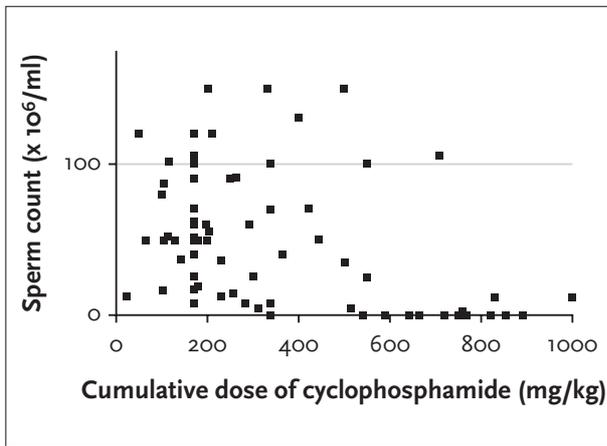
Figure 2
Sperm count in relation to the cumulative dose of cyclophosphamide

Data are derived from five studies that have evaluated sperm count in patients who received cyclophosphamide for idiopathic nephrotic syndrome.[10-14] Evaluation was performed many years after the end of treatment.

cyclophosphamide for malignancies.[16] Notably, these patients also received concurrent therapy with other chemotherapeutic agents and had often received radiotherapy. The study demonstrated that azoospermia developed approximately two to three months after the start of therapy, and was sustained during treatment. Recovery often occurred, and the rapidity and completeness of recovery was dependent on the cumulative dose. Recovery could take three years, but no further improvement was noted after five years. Recovery occurred in more than 70% of patients who received a cumulative dose <7.5 g/m²; in contrast recovery occurred in less than 10% of patients who received >7.5 g/m².

MEASURES TO PRESERVE FERTILITY AFTER CYCLOPHOSPHAMIDE THERAPY

In recent years several options have become available to preserve fertility in women and men, as discussed in detail by Pendse *et al.*[17] Based on observations that the risk of gonadal dysfunction was lower in prepubertal girls, suppression of the ovarian cycle has been advocated as an option. The use of oral contraceptive agents has been claimed to lower the risk of amenorrhoea; however, this claim is based on an uncontrolled study reported in 1981.[18] No more reports have been published since, and well-documented data are lacking. In animal experiments loss of primordial follicles was attenuated by administration of gonadotropin-releasing hormone (GnRH) agonists. These drugs have been successfully used in two studies, one in patients with Hodgkin's disease and another in patients

with SLE. These studies included a limited number of patients, and were not randomised.[17] Still, results look promising, sustained amenorrhoea occurring in 16 of 27 historical controls and in only one of 25 patients treated with a GnRH agonist. Controlled studies are needed to determine the benefits of these agents. Unfortunately, the use of these agents has been associated with flares of SLE disease activity.

Other strategies to preserve fertility in women include cryopreservation of primordial follicles, oocytes, embryos, and ovarian tissue. Thus far, these should be considered experimental therapies.

For male patients cryopreservation of sperm is a well-established procedure to preserve fertility. It is important to realise that the quality of the sperm is often low in patients with systemic diseases even before starting immunosuppressive therapy. Fortunately, newer techniques such as *in vitro* fertilisation (IVF) and intracytoplasmic sperm injection may allow fertilisation with minimal amounts of viable sperm.

A recent study suggested benefits from drug treatment using testosterone to preserve fertility in men.[19] In this small randomised study that included 15 male patients, aged between 23 and 35 years, five received daily oral cyclophosphamide, five received monthly intravenous pulses of cyclophosphamide and five were treated with i.v. cyclophosphamide plus intramuscular testosterone. All patients developed azoospermia during therapy, after six months recovery was noted in all five patients treated with testosterone and in only one of ten untreated patients. Although promising, certainly more data are needed before such an approach can be routinely applied.

IS THE SUPERIORITY OF LONG-TERM I.V. CYCLOPHOSPHAMIDE PROVEN BEYOND DOUBT?

Which regimen is the golden standard?
The use of long-term i.v. cyclophosphamide has been propagated by controlled studies conducted by the National Institutes of Health (NIH).[1-5,20] This 'NIH regimen' has thus become the golden standard in the Netherlands as advocated by the Dutch SLE study group. However, is there a real 'golden standard'? *Table 3* provides an overview of the NIH studies. From the table it is evident that the NIH studies have not used one regimen consistently, rather each study has used a somewhat modified regimen. Thus it is clear that the currently advocated regimen has never been formally tested in controlled trials. Furthermore, it is of interest to note the actual number of patients involved in the NIH studies. In fact, conclusions on the risks and efficacy of long-term i.v. cyclophosphamide are based on data derived from 67 patients in total.

Table 3
The standard NIH regimen: one regimen? Many data?

STUDY	SCHEDULE	PATIENTS (N)
Austin/Steinberg[2]	0.5-1.0 g/m² every 3 months, duration of therapy median 4 years	20
Boumpas[3]	0.5-1.0 g/m² every month for 6 months; thereafter every 3 months for 24 months	20
Gourley/Illie[5]	1.0 g/m² every month for 6 months; thereafter every 3 months for at least 24 months (monthly administration repeated if no improvement after 12 months; quarterly administration continued for 24 months after reaching renal remission	27

Is the superiority of long-term i.v. cyclophosphamide proven?

Most investigators agree that oral prednisone monotherapy is insufficient for patients with SLE nephritis. Newer treatment regimens have, therefore, included alternative immunosuppressive agents such as azathioprine, cyclophosphamide or i.v. pulses of methylprednisolone. It is claimed that the NIH regimen consisting of six monthly pulses of i.v. cyclophosphamide followed by three-monthly pulses for two years, is superior; however, this claim is not supported by the data. In fact, even in a recent follow-up analysis of the NIH data, Illei *et al.* acknowledge that when comparing i.v. cyclophosphamide with i.v. methylprednisolone there were no differences among the treatment groups in risk for death or end-stage renal disease in an intention-to-treat analysis.[5] A difference only became apparent if the definition of failure was extended to include the need for additional immunosuppressive therapy, as more patients in the i.v. methylprednisolone group needed cyclophosphamide treatment at some time point in the course of their disease. Also in the other NIH studies long-term i.v. cyclophosphamide did not result in significantly higher renal survival rates when compared with azathioprine-based regimens or a regimen consisting of short-term i.v. cyclophosphamide (six i.v. pulses only).[1,3,20] Thus, the superiority of long-term i.v. cyclophosphamide is not proven on hard endpoints.

A recent meta-analysis published in the February issue of the American Journal of Kidney Diseases strengthens this conclusion.[21] The use of cyclophosphamide did not significantly reduce the risk of ESRD or death. Admittedly, there was a lower risk of doubling of serum creatinine in cyclophosphamide-treated patients. However, it is debatable whether doubling of serum creatinine is a reliable endpoint. Most controlled studies have used doubling of serum creatinine to define treatment failure and have allowed patients to switch to the alternative regimen at that point of time. If renal insufficiency can be prevented by switching to the alternative regimen, doubling of serum creatinine does not herald ESRD, and thus cannot be considered a hard endpoint. The conclusions of the studies should be read as follows: patients treated with long-term i.v. cyclophosphamide have a lower risk of needing additional

courses of i.v. cyclophosphamide during follow-up. Interpretation of the above-mentioned meta-analysis is also hampered by the fact that the authors have piled the data of studies that used both oral and i.v. cyclophosphamide at dosages ranging from 3 to 50 grams.

Cohort studies including more patients than any of the NIH studies have provided compelling data to suggest that acceptable renal survival rates can be obtained by using regimens that contain no or only limited amounts of cyclophosphamide. Bono *et al.* recently reported an extended follow-up of patients with lupus nephritis treated by Cameron's group at Guy's Hospital.[22] All 110 patients were followed for at least ten years, 64 patients had lupus nephritis class III or IV, and the majority were treated with prednisone and azathioprine. The cumulative incidence of end-stage renal disease was 20% at ten years with no further events thereafter. On reviewing the literature, Bono and Cameron conclude that 'no data to date have demonstrated a superior effect of one immunosuppressive regimen over another when added to prednisone'.

The therapeutic efficacy of a regimen that contained a limited amount of cyclophosphamide is also suggested by Korbet, who has analysed the long-term outcome of patients who were included in a trial that studied the value of add-on plasmapheresis therapy.[23] A total of 86 patients were included in this study in the period 1981 to 1988. Patients were treated with prednisone with added cyclophosphamide in a dose of 2 mg/kg/day for approximately eight weeks. With this regimen a complete remission was obtained in 43% of patients. Notably, remission rate was higher in patients with an initial serum creatinine <124 μmol/l and in white patients. Renal survival was 94% at ten years in the remission group.

Finally, the efficacy of a low-dose cyclophosphamide regimen has recently been proven in two controlled studies.[24,25] The Eurolupus trial was a randomised, controlled study, comparing low-dose cyclophosphamide (six pulses of 500 mg cyclophosphamide every two weeks) with high-dose cyclophosphamide (eight pulses of 750 mg/m² in a one-year period).[24] All patients received azathioprine in the maintenance phase. The proportion of patients who reached a

remission (approximately 80% of patients at 48 months) or remained free of a relapse (approximately 60% at 48 months) was similar in both groups. In a recently published study Contreras *et al.* have compared i.v. cyclophosphamide as maintenance therapy with azathioprine or mycophenolate mofetil.[25] All patients received six monthly pulses of i.v. cyclophosphamide as induction therapy. Event-free survival was lowest in the patients who received cyclophosphamide maintenance therapy. Although the number of patients was small, this study certainly indicates that long-term i.v. cyclophosphamide is not superior.

HIGH-DOSE CYCLOPHOSPHAMIDE AND THE RISK OF RENAL FLARES

It has been proposed that the benefits of high-dose cyclophosphamide may only become apparent after very long follow-up (>10-20 years). Long-term cyclophosphamide may more effectively prevent slow ongoing fibrosis. Furthermore, renal flares were more common in patients receiving short-term i.v. cyclophosphamide.[3] Since the attainment of a complete remission was associated with an improvement in long-term renal survival, renal flares were considered to be early predictors of poor outcome. However, also in this regard the data do not allow such a conclusion. First, the above-mentioned study in which the patients received short-term i.v. cyclophosphamide can be criticised because the patients were not on additional immunosuppressive therapy with azathioprine, which is common practice in Europe. Moreover, in their analysis of the long-term follow-up of the NIH data Illei *et al.* conclude that renal flares do not necessarily result in loss of renal function if treated with additional immunosuppressive agents.[4]

CONCLUSIONS

Patients with lupus nephritis should be advised of the risk of permanent infertility associated with the use of cyclophosphamide. These risks are dependent on the age of the patient and on the cumulative dose of cyclophosphamide. Patients must be advised to seek additional counselling by an obstetrician/gynaecologist. Cryopreservation of sperm is well-established method of preserving fertility. Other measures are currently under study. The available data suggest that patients with lupus nephritis can be effectively treated with regimens that contain no or limited amounts of cyclophosphamide (<10 g). This is particularly so if patients are white and have moderately impaired renal failure. Patients should be warned that additional cyclophosphamide therapy may be needed if disease activity persists or if severe nephritic flares develop. Fortunately, this will only occur in a minority of patients.

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Stopper CARDS II

Wetzels. Cyclophosphamide-induced gonadal toxicity.

Ischaemic preconditioning: from molecular characterisation to clinical application - part I

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ABSTRACT

Ischaemic preconditioning is defined as an increased tolerance to ischaemia and reperfusion induced by a previous sublethal period of ischaemia. Since this is the most powerful mechanism for limiting infarct size, other than timely reperfusion, an overwhelming number of studies have addressed the way in which this form of protection occurs. During the short preconditioning period of ischaemia, several trigger substances are released (adenosine, bradykinin, norepinephrine, opioids). By activation of membrane-bound receptors, these substances activate a complex intracellular signalling cascade, which converges on mitochondrial end-effectors, including the ATP-sensitive potassium channel and the mitochondrial permeability transition pore. Activation of this pathway protects cardiomyocytes against both necrosis and apoptosis during a subsequent more prolonged ischaemic episode. The protection afforded by preconditioning lasts only two to three hours, but reappears 24 hours after the preconditioning stimulus. This 'delayed preconditioning' requires synthesis of new proteins, including inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2) and heat shock proteins. Additionally, preconditioning is not confined to one organ, but can also limit infarct size in remote, non-preconditioned organs ('remote preconditioning'). Knowledge of these mechanisms mediating ischaemic preconditioning is essential to understand which drugs are able to mimic preconditioning or interfere with preconditioning in patients at risk for myocardial ischaemia. This review aims to summarise current knowledge regarding the different forms and mechanisms of ischaemic preconditioning.

INTRODUCTION

Despite major advances in prevention and treatment, ischaemic heart disease, and in particular acute myocardial infarction with its late sequelae, remains the leading cause of morbidity and mortality in the Western world and is rapidly gaining its leading position in the developing world.[1] Moreover, due to improved survival from acute myocardial infarction, more and more patients suffer from chronic heart failure, which is an important late complication of infarction. In this regard, continued improvement of strategies aimed at primary and secondary prevention of myocardial infarction is essential. To define suitable targets for intervention, three factors can be identified that ultimately determine the development and outcome of coronary occlusion.[2,3] The occurrence of coronary artery occlusion is determined by 'vulnerable plaques' (prone to thrombotic complications) and 'vulnerable blood' (prone to thrombosis). Once coronary occlusion has occurred, the clinical outcome is dependent on the 'vulnerability' of the myocardium. Complementary to primary prevention, limitation of infarct size, once occlusion has occurred, is an interesting target which could ultimately attenuate the development of subsequent heart failure.

Until 1986, it was not known whether therapeutic limitation of infarct size was possible at all. In that year, the landmark study by Murry *et al.* was published, in which they described that brief periods of ischaemia (preconditioning ischaemia) in a dog model render the myocardium resistant to a subsequent more prolonged ischaemic period (index ischaemia), since then known as 'ischaemic preconditioning'.[4] Four cycles of five minutes of coronary occlusion prior to 40 minutes occlusion reduced infarct size induced

by these 40 minutes of occlusion by 75% (*figure 1*). However, the infarct sparing effect was lost when three hours of occlusion was applied, emphasising that timely reperfusion remains indispensable for preconditioning to limit myocardial damage. Since than, an overwhelming number of studies have investigated the underlying mechanism, with the ultimate aim of exploiting this powerful protective mechanism in clinical practice. It was found that ischaemic preconditioning offers two windows of protection in time, called 'early' or 'classical' preconditioning, providing protection immediately after the preconditioning stimulus, and 'late' or 'delayed' preconditioning.[5] It was also found that preconditioning ischaemia is able to protect remote cells and organs, which have not been preconditioned by themselves ('remote preconditioning').[6,7] It is essential to realise that most of these studies were conducted in animal models and that important inter-species differences might exist concerning the mechanism of protection, although the effect of preconditioning could be reproduced in all species studied so far.[8] In addition, various *in vitro* and *in vivo* human models have been developed, often using surrogate endpoints to study the effect of preconditioning.[9] This review is the first of two parts that deal with ischaemic

preconditioning. In this first part, we focus on the mechanisms responsible for ischaemic preconditioning. Knowledge of these signalling cascades is essential to understand how various drugs could mimic ischaemic preconditioning or interfere with ischaemic preconditioning. Indeed, many drugs that are currently used in clinical practice have the potential to interfer with ischaemic preconditioning, which is especially relevant in patients who are at risk for ischaemia. In the second part we will focus on this pharmacological modulation of ischaemic preconditioning and we will describe the potential therapeutic applications of preconditioning in the near future.[10]

EARLY ISCHAEMIC PRECONDITIONING

In the original paper by Murry *et al.* it was stated that ischaemic preconditioning reduces infarct size, expressed as percentage of the area at risk, by approximately 75%.[4] Ever since, this has remained the primary endpoint to describe the effect of ischaemic preconditioning. Moreover, using this endpoint, classical preconditioning has limited infarct size in every species tested so far. That this infarct size limitation would, indeed, be able to attenuate the progression to heart failure after myocardial infarction is suggested by the study by Cohen *et al.* who showed that in rabbits early ischaemic preconditioning not only reduces infarct size, but also improves systolic myocardial function, measured three weeks after the index ischaemic insult.[11] For studying ischaemic preconditioning in humans, especially *in vivo*, several surrogate endpoints have been developed, such as ECG changes and coronary lactate, which will be discussed in more detail in the second part of the review. Besides infarct size limitation, ischaemic preconditioning has also been shown to attenuate other forms of ischaemic injury, such as stunning and ventricular arrhythmias, although the evidence is less convincing than for infarct size limitation.[8,12] In the present review, we will focus primarily on necrosis and apoptosis of cardiomyocytes as primary endpoint of ischaemia and reperfusion injury.

The duration of the preconditioning ischaemia as well as the period of reperfusion before the index ischaemia is applied show fairly rigid time frames in order to give full protection. Concerning the preconditioning ischaemic period, protection has been described for periods ranging from one cycle of 1.25 minutes[13] to five five-minute ischaemia/five-minute reperfusion cycles.[14] It is important to realise that the nature of the preconditioning ischaemic stimulus (amount and duration of ischaemic episodes) influences not only the amount of protection but also the signalling pathways involved.[13,15] Too many repetitive stimuli might actually abolish preconditioning.[16] Concerning the reperfusion period before the index ischaemia is applied,
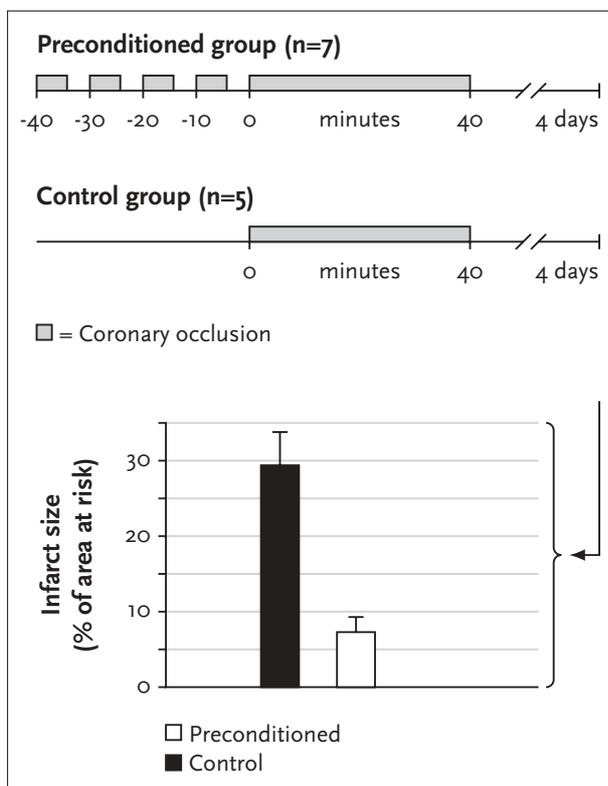
Figure 1
Protocol and results of the original study by Murry et al.[4]
This shows that in the dog heart, four cycles of five-minute coronary occlusion reduced infarct size induced by a subsequent 40-minute coronary occlusion and histologically assessed after four days of reperfusion, by 75%.

the minimum duration lies between 30 seconds and one minute[17] and when the reperfusion period is extended beyond one to two hours, the infarct-limiting effect is no longer evident.[18,19] At this point, it is interesting to mention that in animal models also triggers other than complete ischaemia are able to bring myocardium into the preconditioned state. The observation that myocardium can also be preconditioned by a partial coronary occlusion without reperfusion preceding a sustained period of total occlusion has potential clinical significance considering the nature of thrombus formation in acute myocardial infarction.[20] Also, a brief period of acute volume loading resulting in myocardial stretch,[21,22] a brief period of rapid pacing[23] or transient hyperthermia[24] preceding a sustained period of myocardial ischaemia are all shown to limit infarct size, sharing largely similar signalling pathways as classic ischaemic preconditioning.

In recent years, much research has been devoted to elucidating the mechanisms which are responsible for the preconditioning-induced protection to ischaemia/reperfusion injury. When considering the signalling cascade, triggers and mediators that ultimately converge on end-effectors can be differentiated. Triggers are released during the short preconditioning ischaemia and exert their activity only during this period, whereas end-effectors are solely active during the prolonged index ischaemia and actually cause the protection when needed (*figure 2*).

The first identified and probably most important trigger of classic preconditioning is the endogenous nucleoside adenosine. Myocardial interstitial adenosine concentration increases rapidly during ischaemia.[25] In 1991 it was discovered that adenosine A_1 receptor stimulation during preconditioning ischaemia is essential for protection to occur[26] and that intravenous administration of selective adenosine A_1 receptor agonists instead of preconditioning ischaemia offers similar protection (pharmacological preconditioning).[27] Similarly, local intracoronary adenosine administration offers protection similar to ischaemic preconditioning in dog hearts.[28] Later it was found both *in vitro* and *in vivo* that A_3 receptor stimulation also contributes to ischaemic preconditioning.[15,29] Additional evidence for an important role for adenosine as a trigger of early preconditioning is derived from the observation that pharmacological potentiation of the ischaemia-induced increase in adenosine concentration during preconditioning, by pretreatment with the adenosine-uptake inhibitor dipyridamole, significantly increases the infarct size limiting effect of preconditioning.[30] Considering the protective role of adenosine in ischaemia/reperfusion injury, it is important to realise that, in addition to its role as a trigger of ischaemic preconditioning, endogenous adenosine also provides direct protection against both ischaemia and reperfusion injury, independent of preconditioning, which involves stimulation of adenosine A_{2A} receptors (*figure 3*).[31]
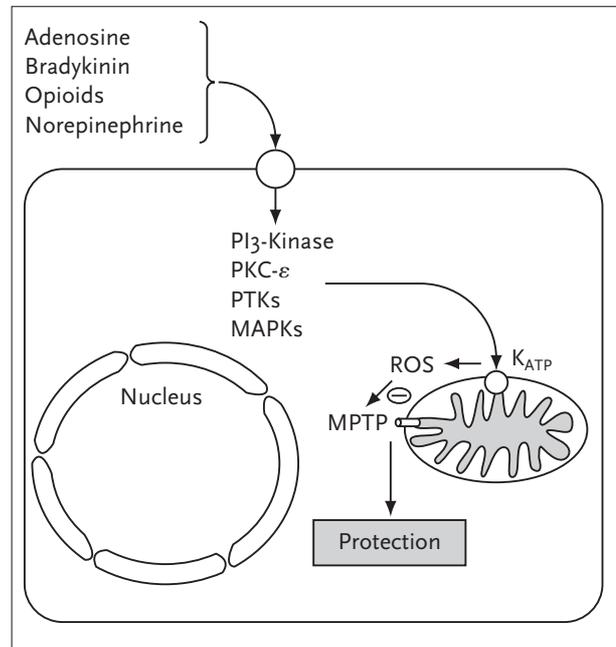
Figure 2

Simplified representation of the mechanism of classical preconditioning

During the preconditioning stimulus, several triggers are released which activate a complex signalling cascade, including phosphatidyl-inositol-3-kinase (PI3-kinase), protein kinase C (PKC), protein tyrosine kinases (PTK) and mitogen-activated-protein kinases (MAPKs). This signalling cascade inhibits opening of the MPTP via mitoK$_{ATP}$ channel opening and ROS formation.
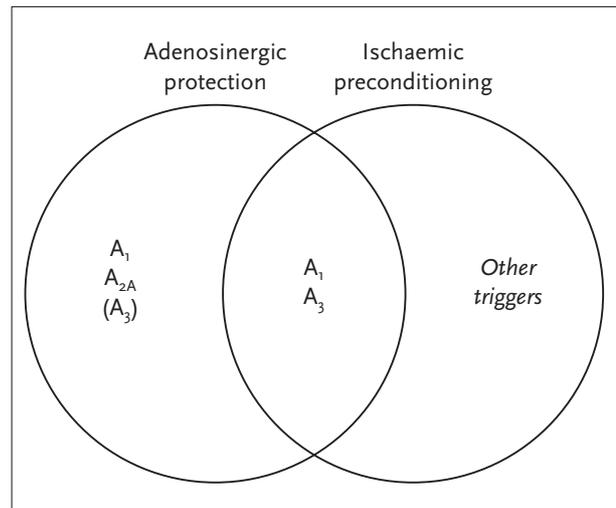
Figure 3

Simplified illustration of the cardioprotection by endogenous adenosine

In addition to the protection afforded by ischaemic preconditioning, adenosine also provides direct cardioprotection during ischaemia and reperfusion.

Riksen, et al. Ischaemic preconditioning.

Later it was found that, in addition to adenosine, several other trigger substances such as bradykinin,[32] opioids,[33] norepinephrine[34] and reactive oxygen species (ROS)[35] are released during preconditioning ischaemia and contribute to the infarct-sparing effect. Regarding ROS, this seems paradoxical, as ROS are generally assumed to contribute to ischaemia/reperfusion injury. Indeed, ROS act as a trigger to protection during the preconditioning stimulus, whereas during the index ischaemia and reperfusion they contribute to injury.[36] Also, a transient elevation in calcium during the preconditioning stimulus might contribute to the protection observed.[37] Whereas an important role for nitric oxide (NO) has unequivocally been shown in delayed preconditioning, its role in classic preconditioning is more controversial. Although exogenous administration of NO donors prior to ischaemia can limit infarct size, endogenous NO-synthase derived NO is probably not involved in classic preconditioning.[38]

It is suggested that because of this redundancy concerning the preconditioning triggers, blockade of one single receptor type only raises the ischaemic threshold required to provide protection, rather than completely blocking protection.[32] Moreover, several studies suggest that the contribution of each of these trigger substances to the induction of pre-conditioning depends on the nature of the stimulus, which should be realised when comparing results from different study protocols.[15,39]

As previously mentioned, it is also possible to pharmaco-logically precondition myocardium. Besides the above-mentioned triggers this can also be achieved with norepineph-rine,[40] endothelin-1,[41] acetylcholine[42] and angiotensin II,[43] but these substances are not released in sufficient quantities during ischaemia to contribute to endogenous protection.

After this triggering phase, an intracellular cascade of events finally brings the cell into its protected phenotype (*figure 2*). Several essential components of this cascade have been identified, although the exact sequence has not yet been fully elucidated. The activation of the intracellular enzyme protein kinase C (PKC) is essential for ischaemic preconditioning.[44,45] Several studies have shown that PKC activation is mediated via activation of phosphatidylin-ositol-3-kinase (PI3K), which is an important upstream signalling molecule.[46,47] PI3K activates the serine/threonine kinase Akt, which subsequently inactivates the proapoptotic kinase glycogen synthase kinase-3 (GSK-3).[48] Following activation, PKC actually translocates from the cytosol to the particulate fraction where phosphorylation of specific substrates can occur.[49] Specific activation and translocation of the isoform PKC-ε seems to be responsible for ischaemic preconditioning.[50] Interestingly, in some animal models only inhibition of PKC during the index ischaemia aborts preconditioning, suggesting that PKC is a mediator and not a trigger.[51] Additionally, activation of a tyrosine kinase mediates early preconditioning, either downstream[52] or in parallel with PKC.[53] Also, each sub-family of the mitogen-activated protein kinases (MAPKs), namely the 42/44-kDa extracellular receptor kinase (ERK), 46/54-kDa c-*jun* kinase (JNK) and 38-kDa p38 MAPK, has been proposed to be involved in the signalling cascade of ischaemic preconditioning (reviewed by Michel *et al.* and Armstrong).[54,55]

Another essential component of the mechanism leading to early protection after preconditioning is the ATP-sensitive potassium channel (K_{ATP} channel). This channel, which opens when intracellular levels of ATP decline, is the known target of sulphonylureas in the pancreas, but is also present in cardiomyocytes and vascular smooth muscle cells. Cardiomyocytes contain K_{ATP} channels located on both the sarcolemma (sarcK_{ATP} channels) and the mitochondrial inner membrane (mitoK_{ATP} channels). These channels have different pharmacological profiles.[36] Both channels are blocked by glibenclamide whereas the mitoK_{ATP} channel is selectively blocked by 5-hydroxydecanoate (5-HD). Diazoxide opens the mitoK_{ATP} channel with far greater affinity than the sarcK_{ATP} channels. Gross and Auchampach first described the critical role of K_{ATP} channel opening in ischaemic preconditioning, because early preconditioning was completely inhibited by the administration of gliben-clamide either before or immediately after the precondi-tioning ischaemia.[56] Initially, sarcK_{ATP} channels were held responsible for preconditioning, but recent evidence increasingly favours a role for mitoK_{ATP} channels (already extensively reviewed).[36,57,58] Several studies have shown that the administration of diazoxide is able to mimic ischaemic preconditioning[59,60] and that 5-HD inhibits precondi-tioning.[61] However, some recent studies still suggest that sarcoK_{ATP} channels are also involved.[62] It appears likely that opening mitoK_{ATP} channels is not only an end-effector of preconditioning, but also a trigger, as opening is also essen-tial during the preconditioning stimulus.[36]

Which end-effectors are involved and how these end-effectors ultimately provide protection is the most elusive part of ischaemic preconditioning. Inhibition of the sodium/hydrogen exchanger, prevention of osmotic swelling and prevention of cytoskeleton disruption by heat shock protein HSP27 have all been proposed to act as end-effectors.[8,63] Lately, however, accumulating evidence strongly suggests that the various upstream signalling pathways all converge on mitochondrial proteins aimed at limiting in particular reperfusion injury. In order to adequately understand this complex part of the preconditioning cascade, we will briefly focus on mitochondrial function, with particular emphasis on the role of mitochondria in reperfusion injury. Although reperfusion is essential for cardiomyocytes to survive a period of ischaemia, it is well appreciated that

reperfusion itself can expedite cell death, which is known as reperfusion injury.[64] The mechanism of reperfusion injury differs from ischaemic injury, best illustrated by the role of apoptosis in both forms of injury. The vast majority of studies on this topic conclude that apoptosis, in contrast to necrotic cell death, only occurs or is accelerated during reperfusion and not during ischaemia.[65,66] Reperfusion is characterised by a boost of ROS, which are important mediators of reperfusion injury, as antioxidants, applied during reperfusion, limit cellular death.[67] Moreover, as apoptosis is an energy-requiring form of cell death, it has been postulated that reperfusion is essential to generate the necessary amount of ATP molecules.[68] Mitochondria play a prominent role in reperfusion. The most important function of mitochondria is the generation of ATP, by the transfer of electrons on oxygen.[69] This transfer is associated with a transfer of H$^+$ions from the inside to the outside of the mitochondrial inner membrane, thus establishing the mitochondrial transmembrane potential. Subsequently, the passive inward flux of H$^+$ions forms the driving force for ATP production. Moreover, during electron transfer, 1 to 5% of ions lose their way and participate in the formation of ROS.[69] The mitochondrial permeability transition pore (MPTP) is formed by multiprotein complexes capable of forming large nonselective pores in the otherwise highly impermeable inner mitochondrial membrane.[70] There is a large body of evidence that this pore, which remains closed during ischaemia, opens during reperfusion.[71] This pore is characteristically opened by high mitochondrial [Ca^{2+}], oxidative stress, ATP depletion and mitochondrial depolarisation, all pre-eminently present during reperfusion.[72] Mitochondrial permeability transition during reperfusion results in uncoupling of the respiratory chain, ultimately resulting in ATP depletion and necrosis on the one hand and in matrix swelling and subsequent rupture of the outer membrane leading to release of proapoptotic proteins and apoptosis on the other hand.[72] That opening of the MPTP indeed contributes to reperfusion injury is convincingly demonstrated by showing that inhibition of MPTP opening at reperfusion, typically with cyclosporine A (CsA), significantly reduces ischaemia/reperfusion injury.[72] A series of recent studies has shown that ischaemic and pharmacological preconditioning ultimately provide protection by inhibiting ROS-induced opening of the MPTP during reperfusion.[73-77] Very recently, an extensive and elegant study by Juhaszova *et al.* showed that ischaemic preconditioning as well as pharmacological preconditioning by a wide variety of drugs act by inhibiting ROS-induced MPTP opening at reperfusion and this study elucidated a great part of the signalling cascade responsible for MPT inhibition.[78] They showed that cardioprotection with a memory (e.g. by ischaemia, diazoxide, pinacidil, bradykinin) opens mitoK$_{ATP}$ channels, resulting in a subtle mitochondrial swelling, which increases electron transport and

gives rise to a small burst of ROS production, which acts as a messenger to activate PKC, which ultimately converge on phosphorylation of GSK-3β. Phosphorylation of GSK-3β inhibits its function and inhibits MPTP opening during reperfusion. Interestingly, GSK-3β can be inhibited by lithium, which has previously been shown to reduce infarct size.[48]

In conclusion, the infarct size limiting effect of ischaemic preconditioning seems to be largely mediated by inhibition of reperfusion injury and subsequent apoptosis. There is convincing evidence that in myocardial infarction, both necrosis and apoptosis are involved.[79] Various animal studies have shown significant reduction in myocardial infarct size using inhibitors of apoptosis, such as caspase inhibitors, during reperfusion.[80-83] Moreover, caspase or endonuclease inhibition after myocardial infarction attenuates ventricular remodelling and improves contractile function.[80,84] Gottlieb *et al.* were the first to show that in an *in vitro* model of rabbit cardiomyocytes, ischaemic preconditioning inhibits ischaemia/reperfusion-induced apoptosis.[85] Later, this was confirmed *in vivo* in a rat model of myocardial ischaemic preconditioning.[14]

With increasing emphasis on the pivotal role of limitation of reperfusion injury in the infarct size limitation by ischaemic preconditioning, several studies explored whether interventions during reperfusion, rather than before ischaemia, could also limit infarct size. This is of great potential importance, as ischaemic insults are seldom predictable and therefore interventions at the time of reperfusion are more suited to most clinical scenarios. Indeed, intermittent short repetitive interruptions to reperfusion at the very onset of reperfusion were shown to provide similar protection to ischaemic preconditioning in dogs and rats, via activation of the PI3K-Akt pathway[86,87] (reviewed by Hausenloy *et al*).[88]

DELAYED ISCHAEMIC PRECONDITIONING

In 1993, it was first described that the protective effect of ischaemic preconditioning, which was previously thought to be a transient phenomenon, reappears 24 hours after the preconditioning ischaemic period and results in a delayed protected phenotype.[5,89] Although not as powerful as the early protection provided by preconditioning (infarct size reduction on average 50%),[5,90] this delayed phase of protection lasts up to 72 hours and, in that respect, might be more therapeutically applicable in clinical practice.[90] Moreover, this late phase of preconditioning also provides robust protection against myocardial stunning.[91] This delayed phase of protection is also called 'late' precondi-

tioning or the 'second window of protection' (SWOP). Although classical and delayed protection largely share common signalling pathways, several essential differences are present (*figure 4*). In this review, we only briefly highlight the differences between classical and delayed preconditioning, the latter being more extensively reviewed elsewhere.[8,92] The distinctive time course of delayed preconditioning and its complete inhibition by protein synthesis inhibitors[93] suggest that synthesis of new proteins is required to obtain the protected phenotype, which is the most striking difference between classical and delayed preconditioning. It is important to realise that the mechanisms mediating protection against infarction and against stunning are not the same, although many pathways are shared, evidenced by the fact that adenosine and K_{ATP} channels play an obligatory role in protection against infarction,[94,95] but not against stunning.[96]

The most important difference between early and late preconditioning regarding the trigger phase is that in delayed preconditioning, in addition to the triggers which are also active in classical preconditioning, endogenous nitric oxide (NO) also provides delayed protection against both stunning and infarction, most likely being derived from endothelial NO synthase (eNOS).[97,98] Subsequently, these triggers initiate a signalling cascade ultimately resulting in increased transcription of cardioprotective genes. Indispensable for this cascade are PKC[99] and, probably downstream to PKC, tyrosine kinases[100] and most likely also other protein kinases, which activate the important transcriptional regulator nuclear factor-κB (NF-κB).[101] Consequently, increased transcription of protective proteins occurs, several of which have been identified so far. Interestingly, NO synthase is also essential during the index ischaemic insult for delayed protection to occur. However, in contrast to the trigger phase in which eNOS is probably involved, during index ischaemia inducible NOS (iNOS) is upregulated and inhibition of iNOS completely abrogates protection during this index ischaemia.[102] Similarly, selective inhibition during the index ischaemia of cyclooxygenase (COX)-2, which was upregulated 24 hours after the preconditioning stimulus, completely blocked protection against stunning as well as infarction.[103] Other proteins that are upregulated and are important in delayed preconditioning are superoxide dismutase, which is an important antioxidant enzyme,[104] and heat shock proteins, although some controversy still exists about the latter.[8] How these upregulated proteins subsequently provide protection against ischaemic injury has not yet been unravelled. However, there is evidence that activation of protein tyrosine kinases is also necessary during the index ischaemia for protection to occur, suggesting a role for post-translational modification of the upregulated proteins.[105] Finally, it is known that opening of K_{ATP} channels during the index ischaemia is necessary for the infarct-sparing effect of delayed preconditioning, whereas delayed protection against stunning does not seem to require K_{ATP} channel opening.[106] The observation that 5-HD during the preconditioning ischaemia inhibits delayed protection favours a role for the mitoK_{ATP} channel rather than the sarcolemmal K_{ATP} channels.[107] Although K_{ATP} channel opening seems to be a final common pathway on which the signalling cascades converge, it is not yet well understood how opening of these channels provides protection. Similar to early preconditioning, several pharmacological interventions are able to trigger delayed protection, mimicking ischaemic preconditioning. In this regard, brief exposure to selective adenosine A_1 and A_3 receptor agonists, exogenous NO donors, ROS-generating substances, bradykinin, δ-opioid agonists and norepinephrine provide delayed protection to infarction.[8] This offers possibilities for future exploitation of this delayed mechanism in clinical practice.
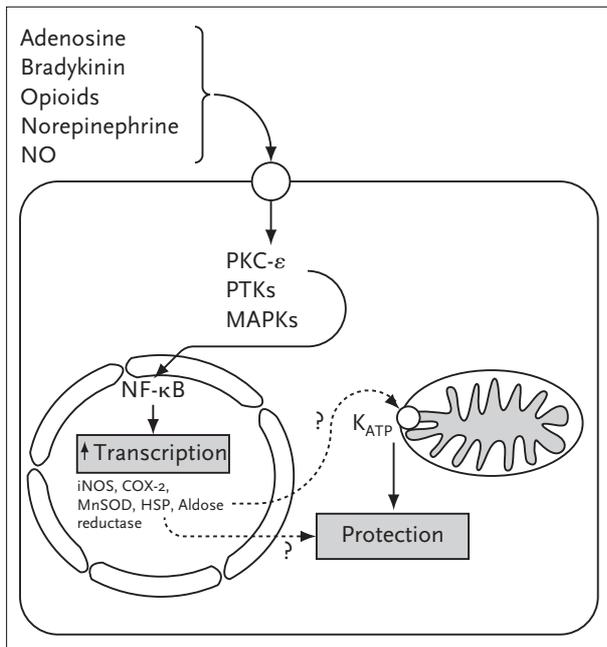
Figure 4
Schematical illustration of the mechanism of delayed preconditioning

In contrast to classical preconditioning, nitric oxide (NO) is an important trigger of delayed protection. Activation of the transcriptional regulator nuclear factor-κB (NF-κB) causes increased transcription of several proteins. Opening of mitochondrial K_{ATP} channels is necessary for the ultimate infarct limitation, but how these channels are opened is still a matter of debate.

REMOTE ISCHAEMIC PRECONDITIONING

In 1993, Przyklenk *et al.* extended the initial view on ischaemic preconditioning tremendously by demonstrating that brief preconditioning occlusions of the circumflex

artery could also limit infarct size from subsequent sustained occlusion of the left anterior descending artery in the dog heart.[6] This was called 'remote intracardiac preconditioning'. Later, it was shown that remote ischaemic preconditioning was not limited to one particular organ system. Transient occlusions of the mesenteric artery limited myocardial infarct size by a subsequent prolonged coronary occlusion,[7,108] since than known as 'inter-organ preconditioning', 'remote preconditioning' or 'preconditioning at a distance'. Since this original finding, remote ischaemic preconditioning of the myocardium has been accomplished by transient circulatory occlusion of the short bowel,[7,109] kidney[110] and hind limb,[111,112] but not of the brain.[113] Similarly, preconditioning the limb in a pig model limited infarct size in several remote skeletal muscles after a subsequent prolonged ischaemia[114] and transient ischaemia of the liver rendered the kidney more resistant to subsequent more severe ischaemia in rats.[115]

Early remote ischaemic preconditioning has been shown in rats,[7] rabbits[116] and pigs,[117] limiting myocardial infarct size to a similar extent as classical preconditioning.[7,112,118] Additionally, a second window of remote protection of the myocardium by applying a short period of preconditioning ischaemia to the small intestine has been shown in rats and rabbits.[116,119,120]

The mechanism underlying remote ischaemic preconditioning is not yet as well defined as the mechanisms mediating classic preconditioning. Interestingly, in the first study on inter-organ remote preconditioning, Gho *et al.* already identified two important clues for understanding the mechanism of protection.[7] First, ganglionic blockade with hexamethonium prior to the preconditioning stimulus abolished cardioprotection, suggesting neuronal involvement. Secondly, reperfusion after the preconditioning ischaemia was essential, suggesting that at reperfusion substances are released in the mesenteric bed that stimulate afferent neurofibres or directly protect the heart. Although several other studies confirmed involvement of a neurogenic pathway in mesenteric preconditioning of the myocardium,[109,121] preconditioning with a more prolonged mesenteric occlusion was not abolished by hexamethonium.[122] Additional evidence that a humoral factor is also involved in remote preconditioning comes from the observation that in rabbits cardioprotection by a preceding short period of coronary occlusion can be transferred to a nonpreconditioned heart via coronary effluent transfusion and even transfusion of whole blood.[123-125] This transferred protection is not mediated via adenosine or norepinephrine in the effluent and can be abolished by the opioid-antagonist naloxone. Additional studies on mesenteric preconditioning of the myocardium showed that capsaicine-sensitive sensory nerves might be involved[116] and that the protection is abolished by pretreatment with naloxone[126] and a bradykinin receptor antagonist[121] before the transient mesenteric occlusion. Moreover, signal transduction via PKC is proposed, based on the findings that inhibition of PKC before as well as after the preconditioning stimulus inhibits protection and that brief mesenteric artery occlusion induces a rapid translocation of PKC-ε from the cytosol to membrane fractions in cardiomyocytes.[122,127] In a rabbit model, it was shown that cardioprotection by a brief renal artery occlusion is totally abolished by adenosine antagonism either before the renal occlusion or before the subsequent coronary occlusion, proposing a dual role for adenosine as trigger and mediator of remote preconditioning.[112,118] In line with these observations, Liem *et al.* recently described evidence that in remote preconditioning with small intestine ischaemia, locally released adenosine triggers afferent nerves which in turn leads to stimulation of cardiac adenosine receptors.[109] Finally, very limited evidence suggests that remote preconditioning also occurs in humans *in vivo*, using a surrogate marker of ischaemic damage. Kharbanda *et al.* showed that three five-minute cycles of forearm ischaemia prevents reduction in acetylcholine-induced vasodilation after 20 minutes of ischaemia of the contralateral arm.[117]

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Bijsluiter

Bijsluiter

Sickle cell disease; a general overview

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ABSTRACT

Sickle cell disease (SCD) is a heterogeneous disorder, with clinical manifestations including chronic haemolysis, an increased susceptibility to infections and vaso-occlusive complications often requiring medical care. Patients with SCD can develop specific and sometimes life-threatening complications, as well as extensive organ damage reducing both their quality of life and their life expectancy. Proven effective treatment options for sickle cell patients are limited to hydroxyurea, blood transfusions and bone marrow transplantation. With the increasing prevalence of SCD in the Netherlands, a fundamental understanding of its pathophysiology and clinical syndromes is of importance for local medical practitioners.

INTRODUCTION

Sickle cell disease (SCD) is clinically one of the most important haemoglobinopathies. It is characterised by haemolytic anaemia, an increased susceptibility to infections and vaso-occlusion that occurs in almost all vascular beds leading to ischaemic tissue injury with organ dysfunction and early death. Outcome is difficult to predict, and few effective therapeutics are available. The prevalence of SCD is on the rise in the Netherlands due to an increased immigration of people from Surinam, the Netherlands Antilles and African countries.[1] A recent survey (with only a 30% response) covering more than 400 Dutch hospital departments where patients with haemoglobinopathies could be registered indicated a population of at least 450 SCD patients (PC Giordano, manuscript in preparation).

This implies that the treatment of sickle cell patients will increasingly be required from general practitioners, internists and haematologists in the Netherlands. Therefore, a fundamental understanding and knowledge of the clinical syndromes of sickle cell patients is of importance for those practicing medicine in the Netherlands. Education of both patients and their families about SCD is also of importance, and the efforts of patient organisations such as the OSCAR (Organisation for Sickle Cell Anaemia Relief; www.sikkelcel.nl) are contributing significantly to the increased awareness of haemoglobinopathies in the Netherlands. This review is not intended to provide specific management guidelines (as can be found in the referenced textbooks and specific papers), but to provide a general overview of some of its major complications and some of the current problems with regard to its general management.

NORMAL HAEMOGLOBIN AND SICKLE HAEMOGLOBIN

The most important protein of red blood cells (RBCs) is haemoglobin, which consists of four globin chains, each folded around a haem molecule. Haemoglobin delivers oxygen from the lungs to the tissues and carbon dioxide from the tissues to the lungs. The predominant haemoglobin in adulthood is HbA (±97%), which consists of two α and two β globin chains ($\alpha_2\beta_2$). Other haemoglobins are HbA$_2$ (2 to 3.5%; $\alpha_2\delta_2$) and HbF (<2%; $\alpha_2\gamma_2$). During intrauterine development, several globin chains are synthesised (α, β, γ, δ, ϵ and ζ), with the predominant haemoglobin type during foetal life being HbF. In the first

12 weeks after birth, the HbF% quickly declines, leaving HbA and HbA_2 as the remaining haemoglobins.[2] The β globin gene is found on chromosome 11p15.5. A single point mutation in the 6th codon leads to substitution of glutamic acid for valine, resulting in an abnormal globin: $β^S$. This results in the formation of 'sickle haemoglobin', or HbS ($α_2β^S_2$). Upon deoxygenation, $β^S$ forms hydrophobic interactions with adjacent $β^S$ globins, ultimately resulting in the polymerisation of HbS. This is the molecular hallmark of SCD.[3] As a consequence, the normally pliable RBC assumes a rigid sickled shape, with ensuing erythrocyte membrane damage and haemolysis. James Herrick, a cardiologist in Chicago, described the first case of SCD in Western literature in 1910.[4] He was alerted by his intern, Ernest E. Irons, about an anaemic black man coping with respiratory problems in whom he noted 'peculiar elongated and sickle shaped' RBC's on a blood smear. The patient was a dental student from Grenada named Walter Clement Noel. After becoming a dentist and practicing shortly in Grenada, Noel died of pneumonia, or possibly an acute chest syndrome (ACS).[5] In the last decades a wealth of information has been produced regarding the potential mechanisms by which the simple $β^S$ mutation leads to the protean clinical manifestations of SCD.

The largest proportion of SCD occurs among blacks, both in Africa and in countries with slave trading histories. In several areas in Africa and in Asia the $β^S$ gene has arisen independently as a new mutation. Recognised by differences in the β globin gene cluster, these haplotypes are named after the areas where they were first described (Senegal, Bantu, Benin, Cameroon and Arab/Indian haplotypes).[6] Inheritance of two $β^S$ genes leads to homozygous SCD, or sickle cell anaemia (HbSS). Other genotypes that give rise to SCD include double heterozygous states in which the $β^S$ gene is inherited together with other abnormal β genes, or with mutations that result in decreased synthesis of β globin genes (β-thalassaemias). In HbC a mutation in the β gene results in substitution of glutamic acid by lysine. The HbSC genotype is the most common double heterozygous state, followed by HbSβ-thalassaemia.[7] People who carry just one $β^S$ mutation have the sickle cell trait (HbAS), and are generally asymptomatic.[8] Hence, the disease is recessive with respect to clinical manifestations, but the gene is dominant in its expression since sickled cells can always be visualised in deoxygenated blood of individuals with HbAS. Combinations of HbAS with β-thalassaemias and of HbSS (or other forms of SCD) with α-thalassaemias (mutations that result in decreased synthesis of α globin genes) give rise to SCD with varying severity depending on the number and type of gene deletions.[7] The survival advantage of people with sickle cell trait with regard to infections with *Plasmodium falciparum* may explain the association of malaria distribution and the distribution of the sickle cell gene, as well as the balanced polymorphism of the $β^S$ gene in the African population.[9,10] In some parts of Africa 45% of the population is heterozygous for the $β^S$ gene and in the United States and the Caribbean about 8% of blacks carry one $β^S$ gene. The $β^S$ gene also occurs in the Caribbean, the Mediterranean basin, Saudi Arabia and in parts of India.[11]

DETERMINANTS OF HbS POLYMERISATION

The pathophysiological hallmark of SCD is intracellular polymerisation of HbS upon deoxygenation.[3] Decrements in pH (which reduce the affinity of haemoglobin for oxygen) enhance HbS polymerisation, as does a rise in temperature.[12] The concentration of HbS in the erythrocytes is also of great importance, with higher concentrations of HbS leading to more rapid polymerisation. Another determinant of the tendency for polymerisation is the presence of other haemoglobins, with HbF and HbA_2 limiting the HbS polymerisation to a greater extent than HbC and HbA. HbSS patients have no HbA, an HbS% greater than 85%, a normal HbA_2% and an elevated HbF%. In people with HbAS, the HbS% is approximately 40%. In HbSC patients the HbS% is about 10 to 15% higher and the mean corpuscular haemoglobin concentration (MCHC) is elevated (due to HbC-induced erythrocyte potassium and water loss), explaining why people with HbSC can be severely affected (as opposed to the largely asymptomatic people with sickle cell trait).[13,14] HbS polymerises effectively with other less common haemoglobin variants such as HbD-$^{Los Angeles}$ and HbO-^{Arab} leading to less frequent double heterozygous forms of SCD.[7] In combinations of HbS and β°-thalassaemia (no β globin synthesis from the affected thalassaemic allele), there is no normal β globin production and hence no HbA. These patients show an HbS% similar to that of HbSS patients (>85%). Inheritance of HbS with $β^+$-thalassaemia (reduced β globin synthesis from the affected thalassaemic allele) leads to a variable HbA% (ranging from 1 to 25%), and hence, a variable HbS%.[7] Combinations of HbSS with α-thalassaemia lead to a slight elevation of the HbA_2% with a concomitant reduction of the HbS%. In patients with HbSβ-thalassaemias and HbSS with α-thalassaemia the mean corpuscular volume (MCV) and the MCHC are reduced, thereby lowering the HbS polymerisation rate as compared to HbSS patients.[6]

CLINICAL MANIFESTATIONS

Sickled erythrocytes get entrapped in the microcirculation, thereby causing ischaemic organ damage throughout the body. For haemoglobin to polymerise in the microcirculation the HbS% and concentration should be sufficiently

Schnog, et al. Sickle cell disease; a general overview.

NOVEMBER 2004, VOL. 62, NO. 10

365

high so that the delay time (Td: the time needed for HbS to form rigid polymers) is shorter than the transit time (Tt: the time needed for erythrocytes to traverse the micro-circulation).[3] In the last decades it has become clear that adhesive interactions between activated vascular endo-thelial cells, erythrocytes, leucocytes and platelets lead to an increased Tt, thereby contributing to the vaso-occlusive process.[15] Also, a proinflammatory state, hypercoagulability and endothelial dysfunction contribute to sickle cell vaso-occlusion.[16-18] If sickled erythrocytes escape the microcircu-lation, the HbS polymer becomes soluble again after reoxy-genation and the red cell can reassume its biconcave shape. However, with repetitive sickling and un-sickling cycles, dense irreversibly sickled cells (ISCs) are formed that are characterised by a significantly reduced lifespan as compared with non-ISCs.[19] From a clinical viewpoint, disease manifestations can be roughly attributed to two phenomena: haemolysis and vaso-occlusion.

Haemolysis

Haemolytic anaemia occurs in all significant forms of SCD, but is less severe in patients with concomitant thalassaemia, HbSC, and/or a high HbF%.[14,20] Red cell survival is esti-mated to be about 17 days in HbSS patients, which is in striking contrast to the 120 days in healthy persons.[19] Intravascular haemolysis in SCD results from complement recognition of sickling-induced membrane changes, cell dehydration and direct membrane damage by rigid haemo-globin polymers.[19] Monocyte and macrophage destruction of physically entrapped cells in the microcirculation also contributes to the shortened erythrocyte lifespan.[21] While there is a great variability between patients, following the decline of the HbF% after birth, the haemoglobin level (and both the haemolytic rate and number of ISCs) remains relatively constant until about 40 years of age. After the fourth decade, haemoglobin levels fall, possibly as the result of declining renal function and marrow failure due to scar-ring and fibrosis.[19,22,23]

The consequences of haemolytic anaemia in SCD are diverse. In order to compensate for the reduced oxygen-carrying capacity, sickle cell patients have a hyperdynamic circulation, an expanded plasma volume, and develop dilated cardiomyopathy at an early age.[24] As the affinity of HbS for oxygen is decreased in comparison with HbA, tissue oxygenation may be relatively preserved (in absence of vaso-occlusion), hence explaining the rather good toler-ance of anaemia in this patient group.[8] Due to the increased erythropoiesis, bone marrow sites that normally become inactivated shortly after birth (such as the skull and femura) remain active.[8] As result of the chronic haemolysis there are increased levels of unconjugated bilirubin, leading to jaundice and a high incidence of pigmented gallstones. Even though these do not usually require surgical removal, laparoscopic cholecystectomy is the most common elective

surgical procedure in SCD.[25-27] Infections with human *parvovirus B19* can lead to life-threatening aplastic anaemia in sickle cell patients.[28]

Vaso-occlusion

Entrapment of sickled cells in the microcirculation leads to tissue ischaemia and damage in almost all organs. This vaso-occlusive process accounts for the majority of SCD-related complications and the affected vascular bed deter-mines its clinical presentation.

The most frequent cause of hospitalisation in sickle cell patients is the *painful crisis*.[29-31] Microvascular occlusion of the bone marrow leads to tissue ischaemia with often excru-ciating pain necessitating hospital admission and treatment with opioid analgesics. Pain is often located in the lumbar spine, femura, ribs, and sternum. Pain is also often located in the abdomen. The aetiology of 'abdominal crises' is not clear. It is diagnosed by ruling out other obvious causes of intra-abdominal pathology. An abdominal crisis can be associated with bowel distension and/or clinical ileus, and may be mistaken for an acute abdominal problem requiring surgical intervention such as appendicitis. Conversely, it has been suggested that appendicitis in SCD is associated with a higher frequency of transmural necrosis due to vaso-occlusion in inflamed tissue.[32,33] Therefore, the threshold for performing abdominal imaging studies in sickle cell patients with abdominal pain should be low. Fever is com-mon during painful crises often without documentation of infection and it mostly resolves without antibiotics. Painful crises may be precipitated by skin cooling, dehydration, infection, or emotional stress, but mostly no specific cause can be identified.[34] Painful crises occur with increased frequency in pregnant women.[34-36] Patients who experience painful crises more often than three times a year have a shorter life expectancy as opposed to those who experience less than three painful crises per year.[30] In children, painful crises often present as dactylitis of the hands and feet ('hand-foot syndrome') and may result in premature closure of the affected epiphysis, leading to shortened deformed bones (*figure 1*).[34] Although not usually life-threatening, painful crises have been associated with sudden death, and can sometimes be followed by an acute multiorgan failure syndrome characterised by worsening of haemolysis, a drop in platelet counts, often encephalopathy and the failure of at least two major organs.[37-39] Pain has a major impact on the quality of life in sickle cell patients, which is underestimated by solely regarding those painful events that require medical care.[40,41] Patients with higher haemo-globin levels (as occurs in patients with concomitant α-thalassaemia) and lower HbF% are admitted more often for treatment of painful crises.[30,35]

A frequent cause of hospitalisation and a leading cause of death is the *acute chest syndrome (ACS)*, which is a clinical syndrome characterised by a new pulmonary infiltrate on

Schnog, et al. Sickle cell disease; a general overview.

NOVEMBER 2004, VOL. 62, NO. 10

366

Figure 1
Shortened digits

Shortened left index finger and right middle finger in a sickle cell patient as a result of a hand-foot syndrome (kindly provided by Professor G.R. Serjeant).

chest X-ray in a patient with either dyspnoea, pleuritic pain, cough or fever and often a fall in the haemoglobin level (*figure 2*).[31,37,42-44] Importantly, it can initially present with a normal chest X-ray or solely with perfusion defects on a lung radioisotope scan. The ACS occurs in 15 to 40% of patients, and often recurs. The aetiology comprises a spectrum of sequestration of sickled cells, fat embolism and thrombosis in the pulmonary vasculature.[43-45] The differentiation of an ACS from pneumonia (which also occurs frequently) is difficult in a sickle cell patient with respiratory symptoms. High fever and purulent sputum favour the diagnosis of pneumonia, whereas worsening of symptoms with progressive hypoxia (despite oxygen supplementation and antibiotic

treatment) with multilobe involvement is highly suggestive of ACS. ACSs are often preceded by painful crises, but painful crises can also occur secondarily to pneumonia (as can ACSs). In a recent landmark study, infectious pathogens were identified in approximately 29% of cases.[44] Atypical micro-organisms such as *Chlamydia pneumoniae* were often involved, as were common bacterial and viral airway pathogens.[44] Risk factors for ACSs are previous ACSs, elevated baseline leucocyte counts and lower HbF%, whereas lower haemoglobin levels are associated with a decreased risk for ACSs.[46] Chronic sickle lung disease, characterised by dyspnoea with both obstructive and restrictive lung disease, as well as by pulmonary hypertension with cor pulmonale, occurs in patients with previous ACS and may be related to extensive fibrosis due to vaso-occlusive injury as well as to *in situ* pulmonary arterial thrombosis (*figure 3*).[39,47-49] Overt *stroke* occurs in up to 11% of patients with SCD before the third decade of life, and is one of its most devastating complications and a leading cause of death.[31,37,50,51] The highest incidence is observed in the first decade of life, with a high recurrence rate.[52,53] Both ischaemic and haemorrhagic stroke occur at all ages, even though ischaemic stroke occurs more frequently in the young, and haemorrhagic stroke is more frequent in patients in the third decade of life.[37,39,52] Occlusion of large vessels due to thrombus formation on narrowed lumina as result of intima hyperplasia is a factor of major importance in the pathogenesis of ischaemic stroke.[54] Cerebral venous thrombosis is also described.[55] Intracranial haemorrhage may be subarachnoid, intraventricular or parenchymal. Risk factors for stroke include low haemoglobin levels, elevated leucocyte
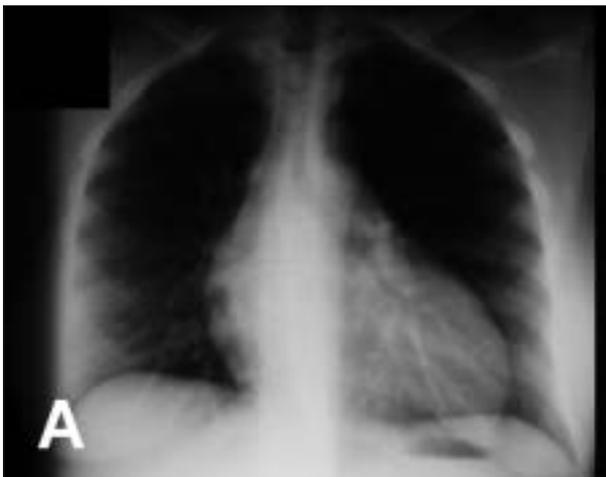
Figure 2
Pulmonary manifestations

Chest X-ray (A) of an 18-year-old HbSS patient during the clinically asymptomatic state. Note the cardiomegaly. Chest X-ray (B) of the same patient several weeks later. During a painful crisis, she developed rapidly progressive respiratory failure with low-grade fever, worsening of haemolysis and chest pain. She refused blood transfusions because of religious beliefs. She died several days later from this episode of acute chest syndrome. No infectious pathogens were identified.

Schnog, et al. Sickle cell disease; a general overview.

NOVEMBER 2004, VOL. 62, NO. 10

367
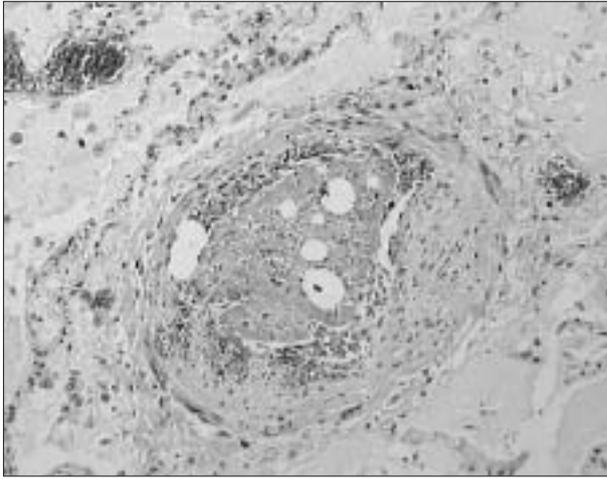
Figure 3
Pulmonary thrombotic arteriopathy

Organising thrombosis in a small pulmonary artery with recanalisation and reactive intimal proliferation in a 37-year-old HbSC patient who died of bacterial sepsis. Such lesions were widespread throughout the lungs.

counts, dactylitis in infants, nocturnal hypoxaemia, a low HbF% and possibly elevated homocysteine levels.[52,56-58] Recent ACSs, as well as frequent ACSs, are risk factors for stroke, as is systolic hypertension.[59,60] The presence of Moyamoya collateral vessels confers a high risk for stroke recurrence, and the increased incidence of stroke in siblings of sickle cell patients with stroke is suggestive of genetic susceptibility within a SCD genotype.[61,62] A marginal protective effect of α-thalassaemia has been reported against both stroke and cerebral vascular abnormalities.[52,63] Cognitive impairment has been associated with ischaemic brain lesions in absence of clinically overt stroke.[64] This silent brain disease may occur in up to a third of SCD patients screened with magnetic resonance imaging and is associated with an increased risk of overt stroke.[65] Central nervous system vasculopathy may be seen in as many as half of the paediatric HbSS patients without clinically overt stroke.[66,67]

Renal dysfunction occurs to some degree in most forms of SCD being a leading cause of death beyond the fourth decade.[37] Due to the extreme interstitial hypertonicity, acidic environment and low oxygen tension of the renal medulla, vaso-occlusion readily occurs in the vasa recta of the kidneys in sickle cell patients and even in subjects with sickle cell trait.[68] This leads to a reduced urine concentrating capacity predisposing patients to dehydration and subsequent vaso-occlusive complications. Patients may suffer from enuresis nocturna. Glomerular injury is common, and may be the result of increased renal blood flow due to the expanded plasma volume and hyperdynamic circulation.[68,69] Severe renal impairment occurs in 4 to 18% of HbSS adults and is often preceded by progressive pro-

teinuria.[70] An incomplete form of distal tubular acidosis is frequently encountered.

The spleen is one of the first organs to be affected in SCD.[71] Blood flow through splenic sinusoids is sluggish, while oxygen tension and pH are low, all favouring the sickling process. In the majority of HbSS infants, a period of hypersplenism is followed by splenic atrophy and loss of splenic function due to vaso-occlusive auto-infarction, whereas splenomegaly (with or without hyposplenism) persists in patients with a high HbF% and in double heterozygous states.[71] *Hyposplenism* renders patients susceptible to overwhelming infections with encapsulated micro-organisms such as *Streptococcus pneumoniae*.[72] Indeed, bacterial infections (pneumonia and meningitis) are still a major cause of death in paediatric patients and pose an important problem in adults as well.[29,39,51] Before splenic atrophy occurs, pooling of blood may lead to severe anaemia and failure to thrive. *Acute splenic sequestration* of blood with life-threatening anaemia is a serious complication with a high mortality rate which occurs before splenic atrophy takes place.[71] Patients in whom the spleen remains anatomically intact remain at risk of this complication. The syndrome presents with massive painful splenomegaly, severe anaemia and cardiovascular collapse.

Painful *skin ulceration* around the ankles is common in patients with homozygous SCD with a peak incidence during the second and third decades of life (*figure 4*).[73] Even though vaso-occlusion contributes significantly to the poor healing tendency, it is probably not the sole aetiological event as it occurs in other haemolytic anaemias as well. Its pathogenesis has not been elucidated. Up to 75% of adult HbSS patients will experience this complication and it also occurs in double heterozygous sickle cell patients.[31]
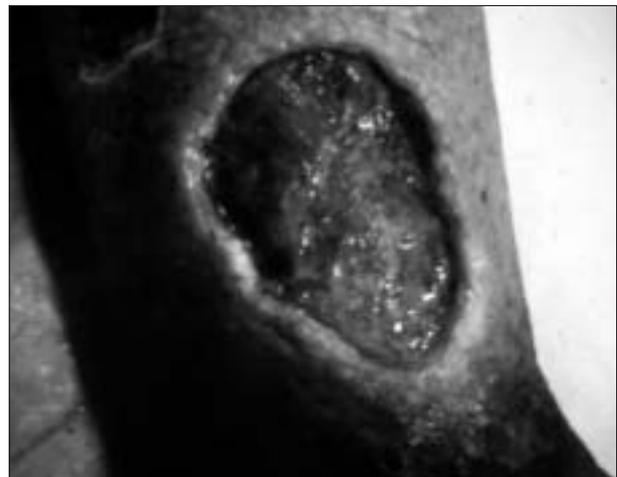
Figure 4
Leg ulcer

Painful nonhealing leg ulcer on the lateral malleolus of a 35-year-old male HbSS patient.

Schnog, et al. Sickle cell disease; a general overview.

NOVEMBER 2004, VOL. 62, NO. 10

368

It occurs more often in males, patients with a low HbF%, and with low haemoglobin levels. Alpha-thalassaemia may be protective for the development of skin ulceration.[73-75] Other important complications related to vaso-occlusion that occur in most forms of SCD include priapism and avascular necrosis mostly of the femoral head.[75] Possibly, myocardial infarction occurs due to obstruction of the coronary vasculature by sickled cells in absence of atherosclerosis.[76-79] Sickle retinopathy is the result of vaso-occlusion in the peripheral retina and is a common complication especially in HbSC patients.[31,80] In order to shunt blood beyond ischaemic retinal areas, progressive neovascularisation and enlargement of pre-existing capillaries occurs. Vitreous haemorrhage is a common complication and may result in blindness. Hyphaema, even when it occurs in people with HbAS, can lead to sudden blindness due to compromised blood circulation with increased intraocular pressure as a result of entrapment of sickled erythrocytes in the outflow apparatus of the anterior chamber.[80] Vaso-occlusion in cochlear structures can result in hearing loss.[81,82] Of the infectious complications, osteomyelitis occurs frequently, especially from *Salmonella*.[11]

DIAGNOSIS

The diagnosis SCD should be suspected in patients presenting with haemolytic anaemia or any of the clinical syndromes described above. Importantly, SCD is not solely confined to individuals of African descent.[83] Haemolytic anaemia, characterised by low haemoglobin levels, reticulocytosis, elevated serum levels of lactate dehydrogenase and low serum haptoglobin levels, is present in all major forms of SCD. The MCV is normal to slightly elevated, while a reduced MCV is indicative of either concurring thalassaemia or iron deficiency. Visualisation of sickled red cells on a routine peripheral blood smear is not seen in sickle cell trait (unless there is severe hypoxia), thus indicating SCD. The presence of Howell-Jolly bodies reflects loss of splenic function.[84] The haemoglobin solubility test can be employed as a rapid screening test for the presence of HbS, but it does not distinguish between the different genotypes. It is based on the demonstration of a haemoglobin precipitate following oxygen extraction. Haemoglobin electrophoresis, high performance liquid chromatography and iso-electric focusing can be used to determine the presence of abnormal haemoglobins. The presence of HbS with an elevated HbF% and absence of HbA indicates either HbSS or HbSβ°-thalassaemia. Patients with HbSβ°-thalassaemia are normally characterised by a reduced MCV, and have a (mildly) elevated HbA$_2$%. In contrast, HbSS patients usually have an MCV and HbA$_2$% in the normal range. Combinations of HbSS with α-thalassaemia can lead to microcytosis with similar haemoglobin patterns as in HbSβ°-thalassaemia. Distinguishing between such genotypes requires family or DNA-based studies such as PCR analysis of known mutations using well defined primers and SSCP (single-strand conformation polymorphism) for unknown mutations. A high HbA% with an HbS fraction above 50% indicates HbSβ+-thalassaemia. In sickle cell trait the HbS% is below 50, but an HbS fraction lower than 35 to 40% is indicative of concurrent α-thalassaemia. The diagnosis HbSC is straightforward, as both HbS and HbC are demonstrated.[84] Importantly, the clinician should realise that recent blood transfusions can result in an erroneous diagnosis.

MANAGEMENT

The management of SCD begins by informing couples at high risk of conceiving children with SCD about the possibilities of prenatal diagnostic testing. Early detection of patients with SCD by newborn screening programmes enables early provision of comprehensive care, which in itself will improve the quality of life and survival of this patient population.[83,85-87] All clinicians caring for patients with SCD should bear in mind that the extent of damage to vital organs is greatly underestimated if one solely relies on clinical manifestations, as was elegantly demonstrated in a landmark autopsy study.[39]

Vaccination against *Streptococcus pneumoniae* (and *Haemophilus influenzae*), as well as penicillin prophylaxis during childhood, have dramatically reduced infection-related mortality in both the USA and Jamaica.[11,87-89] By instructing parents to rapidly seek medical attention when the spleen enlarges and/or with increasing pallor of the skin, the mortality due to splenic sequestration crises and aplastic crises has been significantly reduced in children with SCD.[27,88] Clinical management of painful crisis encompasses rapid pain relief, fluid administration to correct and prevent dehydration, treatment of a potential underlying infection, oxygen supplementation if indicated, and incentive spirometry in patients with thoracic pain to prevent ACSs.[90-92] Managing sickle cell patients with respiratory symptoms can be challenging, as the differentiation between pneumonia and the ACS can be very difficult. A general management strategy could be to treat all patients presenting with a new pulmonary infiltrate with antibiotics (covering common respiratory tract pathogens as well as micro-organisms such as *Chlamydia* and *Mycoplasma pneumoniae*) and supplemental oxygen. With deterioration of the patient's condition or progression of pulmonary infiltrates the diagnosis is more likely an ACS and blood (exchange) transfusions should be immediately instituted.[42,44,93] There are no data regarding the role of anticoagulation in the management of an ACS, but with documentation of thromboembolism anticoagulation is warranted.

Schnog, et al. Sickle cell disease; a general overview.

NOVEMBER 2004, VOL. 62, NO. 10

369

Even though it does not reduce the incidence of acute vaso-occlusive events that require medical care, folate is often prescribed to prevent megaloblastic erythropoiesis.[94] It may be advisable to prescribe folate to all sickle cell patients to reduce at least one easily avoidable potential risk factor for complications by keeping homocysteine levels as low as possible.[56,95] Based upon several clinical observations, it has been suggested that iron deficiency may ameliorate SCD-related symptoms due to lowering of the MCHC. Therefore, worsening of symptoms upon repletion of iron stores in the absence of symptomatic anaemia may justify withholding iron supplementation in selected cases.[96] Regular screening for retinopathy is mandatory, and clinicians caring for sickle cell patients should be aware of specific therapies available for complications such as priapism and leg ulcers, as well as the optimal management of patients undergoing surgery and pregnant patients.[36,73,74,97,98]

Even though many experimental pharmacological therapies have been, and are being studied, only hydroxyurea (HU) has been proven to reduce the incidence of painful crises and ACSs, as well as the transfusion requirement, in highly symptomatic patients.[99,100] HU, a ribonucleotide reductase inhibitor employed in myeloproliferative diseases, has been shown to elevate the HbF% in patients with SCD. The long-term efficacy with regard to both morbidity and mortality in adults has recently been reported, and HU may be relatively safe and effective in preventing complications in paediatric patients as well, although major complications still occur despite HU therapy in both children and adults. Furthermore, it is estimated that 40% of patients do not respond to HU treatment at all.[100-104] HU treatment is not without risk of significant side effects such as myelosuppression and leg ulceration, and the potential risk of malignancies with long-term HU exposure is also a source of concern.[88,101,105-109] Therefore, HU therapy is currently limited to clinically severely affected patients and requires intensive patient monitoring.

For severely affected patients, judicious use of red cell transfusions may be the most powerful therapeutic for preventing major SCD-related complications, and general transfusion guidelines for SCD have recently been published.[110,111] Chronic red cell transfusion programmes aimed at reducing the HbS% below 30% in patients with stroke significantly reduce the risk of stroke recurrence.[88] In children at high risk for first stroke (assessed by detecting abnormal blood flow velocity in large intracranial arteries with transcranial Doppler ultrasonography), chronic transfusions greatly reduce the incidence of a first cerebrovascular event, as well as painful crises and ACS.[110,112] However, such therapies are intensive, the optimal duration is not known, and transfusion-related complications, such as alloimmunisation, infections and iron overload, are of major concern.[101,113] For major surgery (including cholecystectomy), simple pre-operative transfusion is indicated as it reduces the incidence of serious SCD-related postoperative complications.[25,97,114] Clearly, transfusions are not indicated for treatment of uncomplicated painful crises or for correction of steady state anaemia in absence of anaemia-related symptoms or complications (such as heart failure).[111] 'On top' transfusions (administering additional red cell units without removing sickle blood) can precipitate vaso-occlusive complications due to increments in whole blood viscosity, and should be reserved for symptomatic anaemia or severe hypoxemia.[115-117] Exchange transfusions (or erythrocytapheresis if available) are preferred when the patient has a relatively high haemoglobin level and/or is expected to receive multiple transfusions.[115] This results in little net iron gain and keeps whole blood viscosity unchanged. In case of iron overload, stringent adherence to iron chelation therapy is imperative for transfusion therapy to be continued. Expanding the blood donor population of African descent will reduce exposure of sickle cell patients to red cell antigens for which they are mostly negative. Ideally, after extended red cell phenotyping, patients should receive phenotypically matched blood in order to reduce the incidence of alloimmunisation.[118]

In highly selected patients, therapy with bone marrow transplantation (BMT) has resulted in impressive disease amelioration, but carries the risk of major morbidity with a significant risk of mortality.[88,100,101,119,120] Importantly, severely affected young patients (e.g. multiple painful events and/or strokes) with relatively normal heart, lung, and kidney function (without severe residual neurological damage due to stroke) may be eligible for BMT and should be referred to specialised centres in a timely fashion. The implementation of BMT is, however, limited due to donor availability, the poor ability to predict a severe clinical course before significant organ damage has occurred (see below), the morbidity associated with the procedure and the availability of transplant centres. New developments in BMT (such as nonmyeloablative regimens, so called 'mini-transplants') may lead to wider applicability. Gene therapy is being explored in animal models, but is not likely to benefit patients in the near future.[100]

OUTCOME AND DETERMINANTS OF DISEASE COURSE

Life expectancy is on the rise for sickle cell patients, but is still shorter than that of the general population. Male and female patients with HbSS are reported to have a median life expectancy of 42 and 48 years respectively, whereas male and female HbSC patients may survive into the seventh decade.[37,51] However, in some parts of Africa, SCD is still often lethal in childhood.[20] Apart from its somatic manifestations, SCD impacts individuals and their families both socially and physiologically when trying to meet

Schnog, et al. Sickle cell disease; a general overview.

NOVEMBER 2004, VOL. 62, NO. 10

370

the demands of this chronic illness. Due to its unpredictable and debilitating nature, SCD often interferes with educational development as well.

It is generally accepted that patients with an HbSS and HbSβ°-thalassaemia genotype have severe forms of SCD, while patients with HbSβ⁺-thalassaemia and HbSC run relatively milder disease courses. However, both HbSC and HbSβ⁺-thalassaemia patients are not exempt from major SCD-related complications.[30,31,37,39] Alpha-thalassaemia may confer protection for some major clinical events in HbSS patients, but is associated with more pain, whereas in HbSC patients α-thalassaemia may be of overall benefit.[20,31] The SCD modifying effect of α-thalassaemia is more outspoken with a greater number of α gene deletions. Beta-globin gene haplotypes also influence the clinical course of SCD, especially in patients with the Arab/Indian haplotype, which is associated with a higher HbF% and a generally milder clinical course.[20] However, complications occur in all haplotypes, and the interpretation of haplotype effects are obscured by acquired racial diversity of patients. The HbF% rapidly declines in the first months of life, and stabilises early in the first decade.[6] The protective role of a high HbF% is well established, with mortality being higher in patients with a relatively low HbF%.[37,51,121] Especially in patients with 'hereditary persistence of faetal haemoglobin', in whom HbF% exceeds 20%, there are usually no disease manifestations.[20] HbF% tends to be higher in females, which could be a possible explanation for their longer life expectancy.[20,30,37] The protective effect of a high HbF% is relative, as patients with a severe clinical course and a high HbF% have been described, as well as elderly HbSS patients with a low HbF%.[20,38,122,123] Relatively high levels of haemoglobin with a low HbF% are associated with higher pain rates, necrosis of the femoral head, retinopathy and ACS, whereas low haemoglobin levels are a risk factor for brain injury and early death in both children and adults.[20,30,37,46,51,52,58] Children who experience a hand-foot syndrome in the first year of life also tend to experience more major SCD-related complications.[27,58] Leucocytosis in the absence of infection is associated with the occurrence of major clinical events in children such as stroke, and is a risk factor for early death in adults and children.[37,51,52,58] Environmental factors, as well as socioeconomic status, may also influence the clinical course of SCD.[20,121]

CONCLUSION

SCD, in its various forms, is a serious debilitating disease affecting many people worldwide. Chronic haemolytic anaemia and vaso-occlusion in almost all organs leads to significant morbidity and early death. A key issue in managing sickle cell patients is the early identification of high-risk subjects for poor outcome, in order to initiate treatment prior to the development of debilitating organ damage. This is of cardinal importance given the potential side effects of therapeutics such as hydroxyurea, chronic red cell transfusions and bone marrow transplantation. However, it may be concluded from the above that there are currently few reliable objective laboratory tools that can aid the clinician with risk stratification in the daily management of individuals with SCD. Available data regarding the effect of haemoglobin levels and leucocyte counts, as well as epistatic effects of HbF%, β-globin haplotypes and concurrent α-thalassaemia are derived mostly from large epidemiological studies and are difficult to apply to an individual patient. Considerable lack of knowledge still exists regarding determinants of SCD severity, and monitoring sickle cell patients solely by relying on clinical manifestations may also not be accurate. Identification of new risk factors for poor outcome and objective markers for monitoring patients with SCD are needed, as are safer and more widely applicable therapeutics.[40] In this light, it is encouraging that SCD is now included in structural governmental programmes for disease prevention and management in the Netherlands.[124]

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Schnog, et al. Sickle cell disease; a general overview.

NOVEMBER 2004, VOL. 62, NO. 10

371

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NOVEMBER 2004, VOL. 62, NO. 10

372

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NOVEMBER 2004, VOL. 62, NO. 10

373

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NOVEMBER 2004, VOL. 62, NO. 10

374

ORIGINAL ARTICLE

Hypertension management in primary care: standard care and attitude towards a disease management model

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ABSTRACT

**Introduction: Cardiovascular risk control has become one of the hallmarks in the treatment of diabetes and coronary heart disease, yet assessment of individual risk factors is suboptimal. We have designed a new Hypertension Screening Facility (HSF) for the evaluation of cardiovascular risk in hypertensive patients, based on 1) systematic, protocol-driven (WHO/ISH-based) analysis by nurse practitioners, 2) computer-assisted reporting of results and advice, 3) risk assessment using a Decision Support System (DSS), 4) maintenance of the autonomy of the GP. In a pilot study we wanted to investigate this HSF. Methods: Survey 1 addressed a. how general practitioners deal with hypertension, b. whether they intend to and do use existing clinical guidelines, c. what their opinions are towards changes in the current process of care. In survey 2, we evaluated the attitude of GPs using the HSF. Responses were 43% (51 out of 120) to the first survey and 100% (20 out of 20) to the second.
Results: The majority of physicians included lifestyle in their assessment of risk factors and management of hypertension. Consideration of age and a positive family history was extremely high. In contrast, vision disturbances, ECG and microalbuminuria were not often considered. In the absence of additional risk factors, drug treatment was initiated in patients with a mean systolic blood pressure of 162 ± 6 over 99 ± 4 mmHg. In the presence of risk factors (obesity, smoking and a positive family history of cardiovascular disease) treatment is started at an average blood pressure of 154 ± 8 over 96 ± 4 mmHg. Opinions towards a change in management of hypertensive patients were generally positive. The opinions about the new HSF and the cardiovascular risk were reported to the general**

practitioner and considered useful or very useful by 79%. Conclusion: The present study thus confirms that cardiovascular risk evaluation by GPs is suboptimal, but there is a positive attitude towards an improvement in their assessment by HSF. The novelty of the HSF is that it respects the autonomy of the GP and brings the expertise to the GP.

INTRODUCTION

Cardiovascular risk control has become one of the hallmarks in the treatment of diabetes and coronary heart disease, yet assessment of individual risk factors is suboptimal. As illustrated by a population study in the Netherlands, the 'rule-of-halves'[1] is still applicable to the treatment of hypertension.[2,3] International and national protocols are available for the evaluation and treatment of hypertension, and the assessment of comorbidity.[4-7] These protocols and the availability of efficient drugs are in contrast with the insufficient control of hypertension.[8-12]
At first glance hypertension management protocols such as provided by the World Health Organisation (WHO) seem straightforward.[4] Nevertheless, in many countries, physicians are primarily involved in curing rather than preventing disease and preventive work therefore requires reorganisation of medical practice.[13-15] Furthermore, it could be argued that the information the general practitioner (GP) needs to deal with is too complex, changes too quickly and imposes too great a workload. A potential solution to deal with protocols to manage hypertension and prevent cardio-

vascular disease in a detailed manner is the application of a Hypertension Screening Facility (HSF).[16-18] This concept supplies systematic assessment and management of hypertensive patients according to guidelines and yields complete assessment of coexisting cardiovascular risk factors and advice for the general practitioner.[19] A computer-based decision support system (DSS) has been shown to further improve the quality of antihypertensive treatment.[20,21] We designed a new strategy for the identification and evaluation of cardiovascular risk factors in hypertensive patients and have implemented it in our clinic since 1997. The strategy is based on 1) a systematic, protocol-driven (WHO/ISH-based) analysis by nurse practitioners, 2) computer-assisted fast reporting of results and advice, 3) risk assessment using a DSS and 4) maintenance of the autonomy of the GP. Here, we report on two surveys. The first addressed the question how general practitioners judge their own management of hypertension, whether they intend to and do use existing clinical guidelines, and what their opinions are towards assistance in the current process of care. The second evaluated the attitude of GPs using the HSF.

METHODS

Survey 1: Current hypertension management and cardiovascular risk assessment by GPs

For the first study, data were obtained by sending a questionnaire to 120 general practitioners in the second half of 1999. All physicians worked in the close vicinity of the HSF. The physicians received a covering letter explaining that in the region a new disease management strategy was being developed for hypertension.

The questionnaire consisted of 31 questions, concerning the assessment of hypertension and risk factors, and drug treatment. Furthermore, the GPs were asked for their opinions on the disease management model. The questions about assessment of hypertension, risk factors and target organ damage closely followed the issues addressed in the WHO-ISH.[4] The questions are listed in the on-line table (www.nephrogenomics.net/data/appendices). The general practitioners were asked to estimate how frequently they closely adhered to the protocols as supplied by the Dutch College of General Practitioners. Regarding drug treatment, preferences for particular groups of drugs were assessed in general, and related to two hypertensive states: essential hypertension without risk factors and essential hypertension with three risk factors (obesity, positive family history of cardiovascular disease and smoking). The physicians received a brief description of the new HSF, and they were asked how frequently they would use the HSF and what they expected from the facility.

Risk assessment using an HSF

In December 2000 the facilities of our HSF were made available to 20 general practitioners. Hypertensive patients of these physicians could attend the facility for a complete assessment of the history, including assessment of cardiovascular risk factors and symptoms of target organ damage. A complete physical examination was performed, including clinic blood pressure, 24-hour ambulant blood pressure measurement and electrocardiogram (ECG), blood sampling for routine chemistry and risk factor determination. Furthermore, creatinine clearance and microalbuminuria were measured. Cardiovascular risk was estimated based on WHO guidelines[4] and using a DSS. The DSS consisted of a set of rules formulated in Visual Basic (see online appendix at www.nephrogenomics.net/data/appendices). The data needed to classify the patient were extracted from the HSF database. Primary and secondary prevention strategies for the patient are formulated by the nurse practitioner and checked by a hypertension specialist. Test results, cardiovascular risk estimation and prevention strategies were reported to the GP, who decides on the (non)pharmacological treatment and continues follow-up of the patient.

Survey 2: Opinions about the HSF

In our second survey we assessed the opinion of GPs after using the HSF for almost a year. Data were obtained by sending a questionnaire to the 20 general practitioners. The questionnaire consisted of 20 questions concerning attainability and service of the HSF, indications for using it, opinions about usefulness of different aspects of the analysis and whether the GP agreed with the advice given and implemented the suggested treatment.

RESULTS

Survey 1: Hypertension and cardiovascular risk assessment

The response was 43%. Characteristics of the respondents are summarised in *table 1*. *Table 2* lists the general aspects of hypertension assessment. Of the physicians who responded, 80% said they used the guidelines of the Dutch College of General Practitioners. The majority of physicians included lifestyle in their assessment of risk factors and management of hypertension (*figure 1*). Consideration of age and a positive family history was extremely high. In contrast, vision disturbances, ECG and microalbuminuria were not often considered in the assessment of a hypertensive patient. Most physicians answered that they were more aggressive in their approach if one or more risk factors were present. No correlation could be demonstrated, however, between the frequency of assessing risk factors and end-organ damage for each GP and the level of blood pressure where therapy was initiated by that GP.

Wassenberg, et al. Hypertension management in primary care.

NOVEMBER 2004, VOL. 62, NO. 10

376
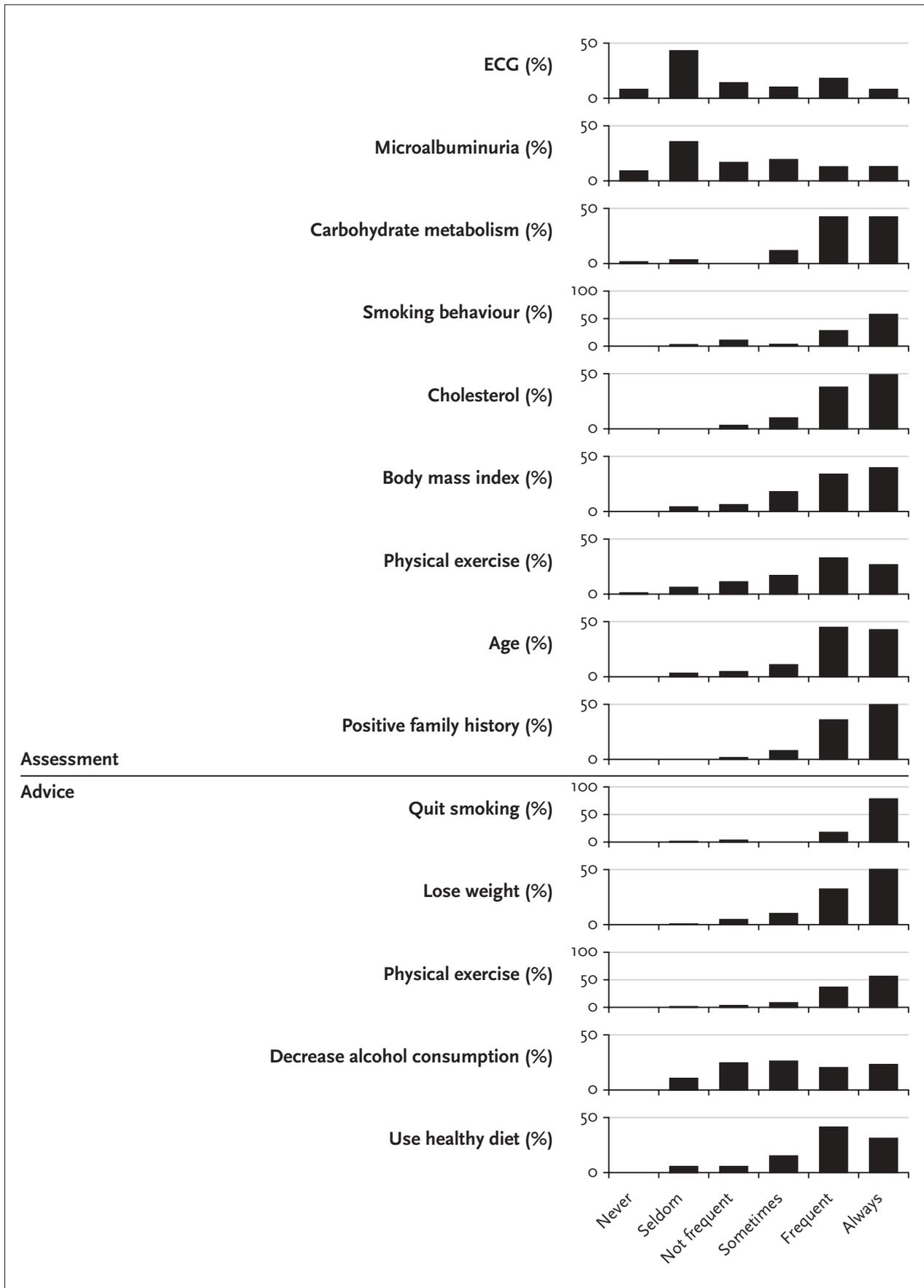
Figure 1

Risk factors and target organ damage and nonpharmacological intervention

Wassenberg, et al. Hypertension management in primary care.

NOVEMBER 2004, VOL. 62, NO. 10

377

Table 1

Characteristics of the respondents

Sent questionnaires		120
No. respondents		51
Age (years)	30-40	16
	40-50	47
	50-60	34
	>60	4
Form of practice	Single GP	51
	Two GPs	29
	Group	20
Supporting workers present	Physical therapy	14
	Dietician	10
	Social worker	8

Data shown as percentage of respondents.

Table 2

Assessment of hypertension

% of patients in whom blood pressure is assessed[1]		33
Person who measured blood pressure		
	Physician	86
	Assistant	12
	Nonresponders	2
Means of measurement		
	Mercury system	41
	Different manual	55
	Automatic device	2
	Nonresponders	2
No. measurements before starting treatment		
	2	8
	3	69
	4	14
	>4	2
	Nonresponders	2
Time interval between measurements		
	1 week	8
	2 weeks	63
	4 weeks	14
	> 4 weeks	8
	Nonresponders	2
Adherence to protocol for the assessment of hypertension[2] (median)		80

[1]*Median percentage of patients that visit. The other data shown are percentages of respondents.* [2]*The protocol advises measuring blood pressure on at least three occasions (excluding the first measurement) in a period of several weeks to several months, depending on the blood pressure level.*

When one antihypertensive drug was used, there was a preference for β-blockers, ACE inhibitors and diuretics (in that order), while angiotensin-receptor blockers (AT-1 blockers), calcium antagonists and α-blockers were infrequently chosen. When two drugs were applied, diuretics were frequently combined with β-blockers or ACE inhibitors. Other combinations were less popular. Data on drug treatment are summarised in *figures 2* and *3*.
In the absence of additional risk factors, drug treatment is initiated in patients with a mean systolic blood pressure

(SBP) of 162 ± 6 mmHg or diastolic blood pressure (DBP) of 99 ± 4 mmHg. In the case of a 45-year-old obese, smoking patient with a family history of cardiovascular disease, drug treatment is instituted at an average SBP of 154 ± 8 mmHg and DBP of 96 ± 4 mmHg. The physicians preferred β-blockers, ACE inhibitors and diuretics as the drug of choice for treatment of patients without risk factors for cardiovascular disease (*figure 2*). ACE inhibitors, β-blockers and diuretics (in that order) were preferred for high-risk patients (*figure 3*). The majority of GPs replied that they used the guidelines of the Dutch College of General Practitioners frequently (29%), very frequently (29%) or always (8%).

Survey 1: Attitudes towards a change in hypertension management
The last questions in the questionnaire addressed the opinions of the GPs regarding using a new HSF. Of the physicians, 8% answered that they would always use the facility, 43% often and 24% sometimes. In contrast, less GPs answered that would seldom (10%), hardly ever (12%) or never (4%) use a hospital outpatient HSF. The completeness of the assessment would be a main reason for the use of such an HSF, while time constraints were less important.

Survey 2: Opinions about risk assessment using an HSF
The response to this questionnaire was 100%. All physicians had used the HSF for one or more of their patients. A majority of these physicians indicated that they used the facility for patients with inadequately controlled blood pressure (*table 3*). The other reasons for the use of the HSF were analysis of newly diagnosed hypertensive patients, young patients, and patients who were suspected of having secondary hypertension.

Table 3

Main reasons for using the Hypertension Screening Facility

Inadequately controlled blood pressure	93%
Assessment of newly diagnosed hypertension	43%
Young patients or possible secondary cause of hypertension	36%

Percentage of physicians (n=20) stating they used the facility for the reasons mentioned.

Results of the investigations to determine cardiovascular risk were reported to the GP and considered useful or very useful by 79%. Of the GPs, 93% reported the assessment of target organ damage as being useful or very useful and 86% rated the analysis of secondary hypertension as useful or very useful. The advice on antihypertensive medication,

Wassenberg, et al. Hypertension management in primary care.

NOVEMBER 2004, VOL. 62, NO. 10

378
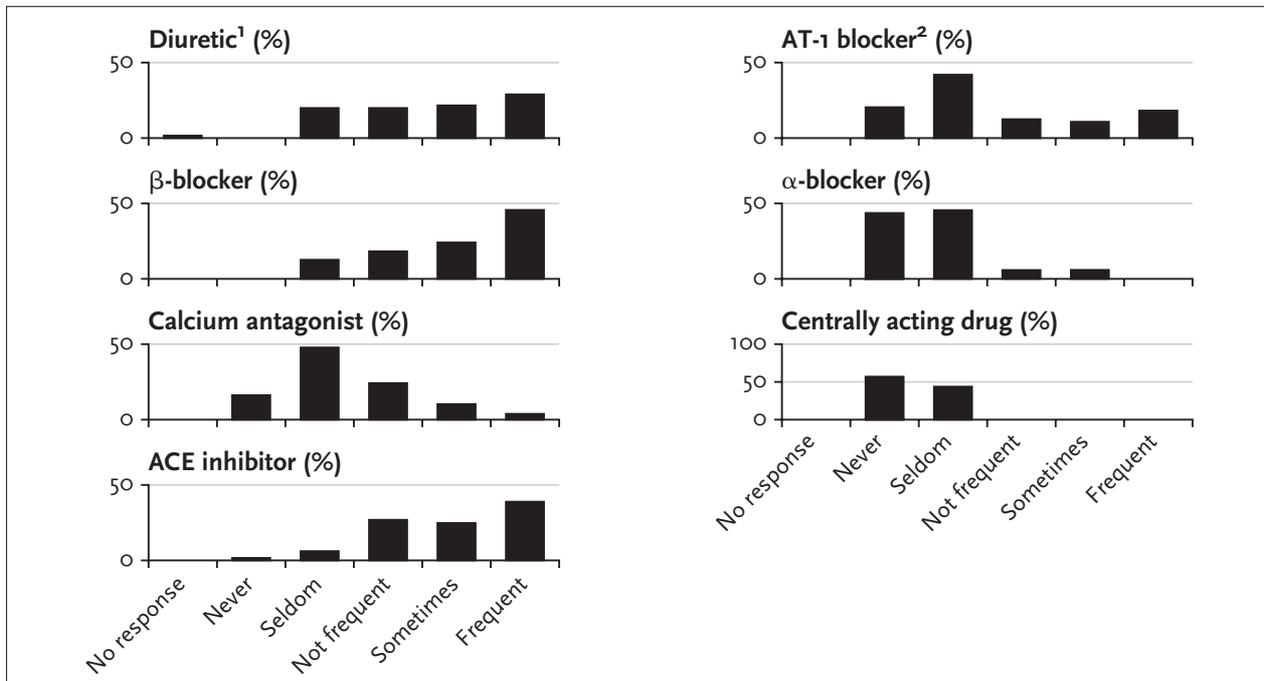
Figure 2
Drug therapy: monotherapy

[1]The guidelines of the Dutch College of General Practitioners list thiazides as first choice, except in case of diabetes with microalbuminuria (ACE inhibitor) and coronary artery disease (β-blocker). [2]It should be noted that the guideline does not mention the use of AT-1 blockers. Data shown as percentage of respondents who state they use a particular drug (or combination).

including first-line drug treatment choice and dosage, was rated as useful by 64% of respondents and as very useful by 29%. The analysis of the HSF also summarises contra-indicated medication, which was considered useful in 71% and very useful in 14% of respondents.

In total 86% of the GPs followed the advice of the HSF on management of the patient most of the time, while 14% always followed the advice. Of the respondents, 29% reported that using the HSF was less time consuming, 36% noted no difference and 21% reported that it was more time consuming. Quality of patient care improved with use of the HSF according to the judgement of 86% of the GPs and 93% intended to use the facility in the future.

DISCUSSION

Standard preventive care concerning cardiovascular disease in the Netherlands is mainly supplied by GPs. The present study assessed how GPs judge their own management of hypertension, whether they intend to and do use existing clinical guidelines, and what their opinions are towards assistance in the current process of care. Furthermore, the attitudes of GPs using the HSF were evaluated. Despite the fact that most of the responders answered positively to the question whether they followed the guidelines, separate aspects of the analysis revealed otherwise. In particular,

target organ damage was not completely routinely assessed. Although blood pressure levels at which hypertension treatment was initiated varied widely, levels were close to the levels in the guideline provided by the Dutch Association of General Practitioners. The GPs were willing to apply a screening by an HSF, and the facility was judged positively after it was implemented.

The average blood pressure thresholds these GPs used to initiate pharmacotherapy were slightly lower than the thresholds recommended by the Dutch College of General Practitioners (SBP 180 mmHg and DBP 105 mmHg in the absence of risk factors). However, these values largely exceed the levels recommended in the guidelines of the WHO, the Joint National Committee guidelines and the European Hypertension Society.[4,5,22] Considering treatment, there was a preference for β-blockers, ACE inhibitors or diuretics. When two drugs were applied, diuretics were preferentially combined with β-blockers and ACE inhibitors. Most GPs preferred to prescribe β-blockers and ACE inhibitors instead of diuretics, recommended as first choice by the Dutch College of General Practitioners.

Cardiovascular risk factors and lifestyle were assessed by almost all GPs. However, target organ damage was mostly not considered; in particular, microalbuminuria, ECG and other indicators of target-organ damage were not assessed. These results support the view that classical disease management may underestimate the overall cardiovascular risk

Wassenberg, et al. Hypertension management in primary care.

NOVEMBER 2004, VOL. 62, NO. 10

379
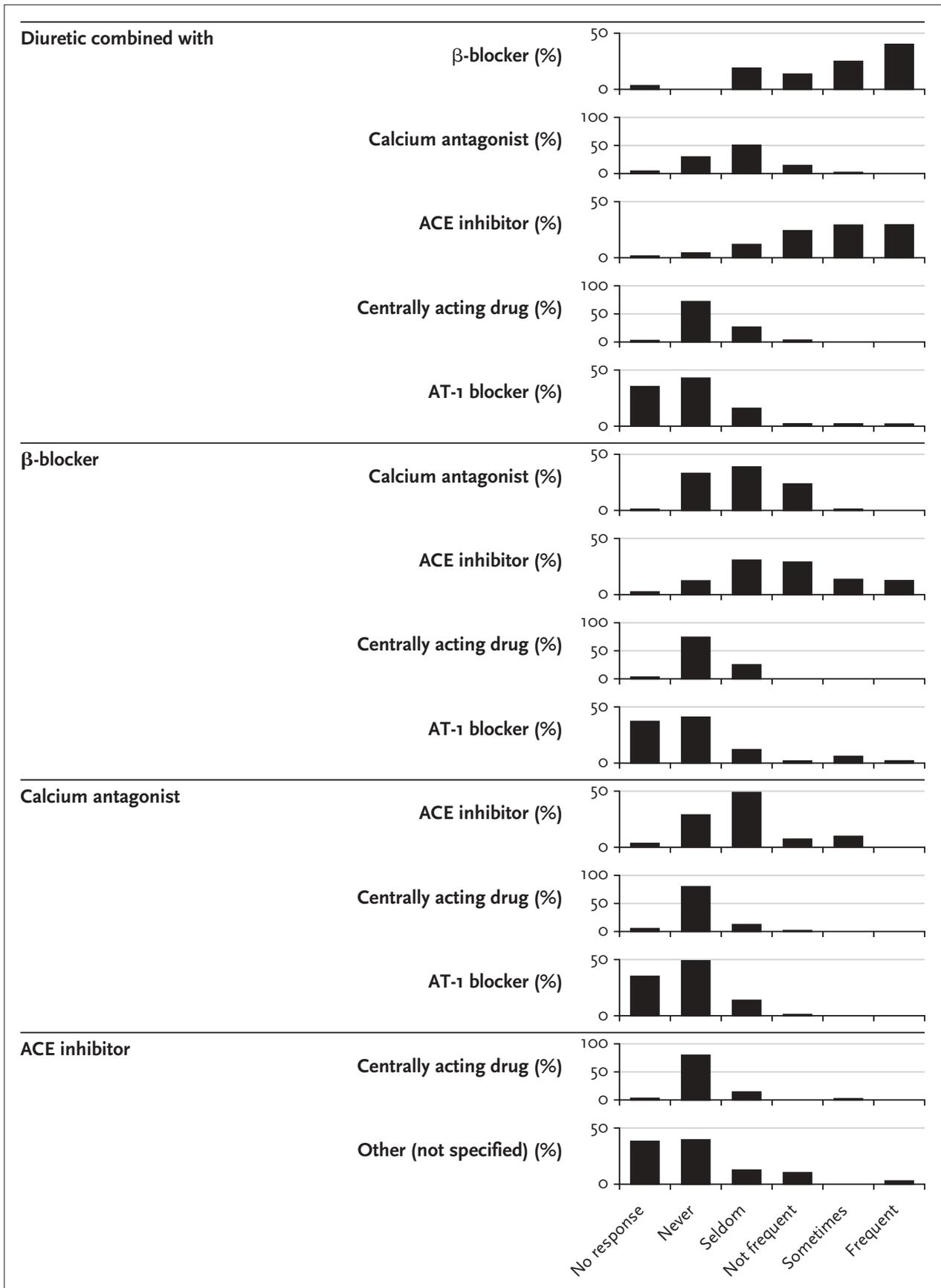
Figure 3

Drug therapy: duotherapy

Data shown as percentage of respondents who state they use a particular drug (or combination).

of patients presenting with hypertension and stress the importance of improving disease management. Also other studies have shown there is an underestimation of risk and considerable room for improvement of primary and secondary prevention.[15,23]

In our study 80% of GPs stated to work according to the guidelines of the Dutch College of General Practitioners concerning the *assessment* of hypertension; however, only 66% of the physicians report using the clinical guidelines concerning hypertension *treatment*. This means that a significant proportion of GPs have not implemented the guideline of the Dutch College of General Practitioners. Although a majority of the GPs intended to work following guidelines, adherence appeared doubtful.[10,24,25]

The question arises why guidelines are so hard to follow in practice. Other research has focused on whether a change in a guideline was indeed followed by a response of GPs to implementations in their medical assessment and treatment.[26-31] Many reasons can be envisioned. Some of the obstacles to following guidelines are related to the physician himself and to the organisation of primary care: high workload,[28] dated knowledge on cardiovascular risk assessment,[28] availability of laboratory tests and ECG equipment and interpretation. Whereas guidelines may seem obvious, they contain many items that can not be easily dealt with in the speed of practice. A reflection of this is found in the most prominent response to the question why the HSF would be used: completeness of the screening. The present approach using the HSF assists in such complete analyses, without referral to a hospital, which may have negative side effects for the patient.

Our study underlines that GPs prefer to treat their own hypertensive patients and refer patients mainly for additional diagnostic procedures or pharmacotherapeutic advice. The majority of hypertensive patients were referred to an internist when the GP suspected secondary hypertension, target organ damage or when there was refractory hypertension. Most of the GPs do not refer with the goal of leaving treatment to the internist. Leaving intact the autonomy of the treatment by the GP has been recognised as a important issue for GPs in other settings, in particular the introduction of evidence-based medicine guidelines.[32] Of the GPs, 75% stated that they would use an outpatient HSF particularly to obtain a more complete assessment of cardiovascular risk in the hypertensive patient. The opinions towards changes in the current design of care of hypertension were positive.

As assessed by the second survey, the alternative approach of hypertension management was readily accepted by a subgroup of GPs in the region who had been using the HSF. Furthermore, the survey shows that the assessment of their patients by the HSF was considered useful. Of the physicians 86% reported that quality of patient care had improved. Hopefully this new method of disease management will lead to an improvement of objective risk calculation and a reduction in undertreatment of the different risk factors for cardiovascular disease in primary care patients. One of the hallmarks of the current approach is that the HSF provides a systematic assessment of cardiovascular risk and gives (pharmaco)theurapeutic advice. Importantly, the unit does not initiate the therapy. In conclusion, the present study confirms that cardiovascular risk evaluation by GPs is suboptimal. It also demonstrates that the attitude of GPs to improve their assessment by using an HSF is positive. The novelty of the HSF is that it respects the autonomy of the GP and brings the expertise towards the GP.

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NOVEMBER 2004, VOL. 62, NO. 10

381

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Bijsluiter

Wassenberg, et al. Hypertension management in primary care.

Quality of life and metabolic control in patients with diabetes mellitus type 1 treated by continuous subcutaneous insulin infusion or multiple daily insulin injections

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ABSTRACT

Objective: To assess the quality of life and metabolic control in patients with diabetes mellitus type 1 on continuous subcutaneous insulin infusion (CSII) in comparison with patients on multiple daily insulin injections (MDII).

Research design and methods: The study included 49 patients (13 males, 36 females), aged 41.4 ± 11.3 years (mean ± SD) on CSII for >1 year and 79 patients (43 males, 36 females), aged 43.1 ± 14.8 years on MDII for >1 year, from three Dutch diabetic clinics. There were no statistically significant differences in duration of diabetes, social class, level of education, marital status, smoking or recent admissions to hospital. The questionnaires used were a Diabetes Quality of Life scale adapted from the DCCT, the Diabetes Satisfaction Questionnaire (DTSQ), and the WHO Well-Being Questionnaire. HbA_{1c} was measured with an HPLC method (reference range 4.3 to 6.1 %).

Results: Using two-sided t-tests no statiscally significant differences were found between the patients on CSII and MDII with respect to quality of life (version A (<30 years) 4.32 ± 0.22 *vs* 4.20 ± 0.30; version B (≥30 years) 4.18 ± 0.25 *vs* 4.29 ± 0.28), well-being (48.59 ± 9.23 *vs* 50.99 ± 8.70), satisfaction with treatment (5.10 ± 0.69 *vs* 5.15 ± 0.71) and HbA_{1c} (8.14 ± 1.51 *vs* 8.47 ± 1.40). Frequency of daily blood glucose monitoring was slightly higher in CSII than in MDII patients (4.52 ± 1.19 *vs* 3.60 ± 1.47; p<0.0001).

Conclusion: The present data indicate that patients on CSII have similar QoL based on questionnaires when compared with patients on MDII. These data suggest that in patients with less optimal control on MDII, converting the treatment strategy to CSII is not associated with decreased quality of life.

OBJECTIVE

Over the last ten years, treatment with continuous subcutaneous insulin infusion (CSII) has become more popular, probably for a large part due to a more flexible lifestyle and a better quality of life. The great improvement in insulin pumps (for example, better technology, lighter and smaller devices) as well as the material (needles, catheters, gips, etc.) has made continuous subcutaneous insulin administration much easier. Although the multiple daily insulin injection (MDII) strategy has proven its benefits regarding diabetes control and complications, one of the remaining and important concerns is the frequency of hypoglycaemia events probably caused by the unpredictable absorption of subcutaneously injected insulin.[1,2] CSII therapy has probably solved this problem. CSII has been shown to improve glycaemic control as compared with MDII in reasonably well-controlled diabetes patients (0.35% HbA_{1c}).[3-5] In ad-

dition, in patients with poor metabolic control a 0.8% HbA$_{\text{IC}}$ improvement in metabolic control was recently shown.[6] Moreover, several studies have shown an advantage in glycaemic control in CSII-treated patients with the use of a rapid-acting insulin analogue instead of unmodified human insulin.[7,8]

However, even with these improvements, many diabetologists still regard CSII therapy as the last resort in insulin treatment for patients with diabetes mellitus. One of the reasons for this could be the idea that CSII therapy is a psychological burden for the patient. This, however, is not supported by systematic studies. Some initial and small studies suggest a better quality of life with insulin pump treatment, especially when compared with conventional insulin treatment (for example, therapies consisting of twice-daily insulin mixtures) but show less or equal benefit when compared with MDII. These studies were performed with the older, currently outdated equipment and measured different aspects of quality of life, such as depression and anxiety separately.[3,9-14]

The aim of the present study was to compare the quality of life (QoL) in patients with diabetes mellitus type 1 on CSII to that in patients on MDII. To do so, we performed a cross-sectional study on items of QoL in two groups of patients with diabetes mellitus type 1 either treated with CSII or with MDII and who had been stable for a long time.

RESEARCH DESIGN AND METHODS

Patients with diabetes mellitus type 1 who had been stable for at least one year on insulin pump therapy were recruited from three different hospitals. In the three hospitals all patients with diabetes mellitus type 1 were treated with MDII (in total 945), and 95 patients were treated with CSII. At the time of the original cross-sectional study no patients with diabetes mellitus type 2 were treated with CSII and since at that time insulin analogues were only available for clinical trial purposes, no patients were treated with these new types of insulin. In total 55 patients using CSII were invited to an information evening on new developments in insulin pump treatment. Of these patients, 49 responded and they were asked to fill in a number of questionnaires. In each hospital twice as many patients with MDII were randomly selected and asked to fill in the questionnaires before the regular outpatient visit. In this group a total of 79 patients were recruited. Included patients had to have been treated with MDII or CSII for at least one year. Patients with a documented mental disorder were excluded from the study.

The patients received the questionnaires from their own physicians. All questionnaires were returned for analysis together with the most recent HbA$_{\text{IC}}$ value of the patient.

Patients spent about 30 minutes filling in the questionnaire. There was a general section, consisting of sociodemographic data, such as age, sex, marital status, education, smoking behaviour and more specific questions concerning the duration of diabetes, number of hypoglycaemic events, and number of blood sugar controls daily. In addition three quality of life measurements were carried out.

The quality of life for diabetic patients (DQOL)

This questionnaire measures the current situation, the influence of having diabetes on daily functioning and the worries arising from it. The questionnaire consists of four subscales: satisfaction, impact, worries associated with diabetes and worries in general. There are two versions of the last subscale: version A is for persons younger than 30 years and version B for 30 years and older. The subscale 'satisfaction' contains 23 items, the subscale 'impact' 20 items, the subscale 'worries' associated with diabetes 16 items and the subscale 'worries in general' version A 10 and version B 9 items. In total, the questionnaire comprises 69 (version A) or 68 items (version B). A five-point scale is used in the DQOL, ranging from 1 (very unsatisfied) to 5 (very satisfied) or from 1 (never) to 5 (always). A high score on the DQOL means that the individual is very satisfied, the impact of diabetes on daily functioning is not experienced as strong and he/she has few general and diabetes-related worries. The internal consistency of the version A questionnaire was 0.9 and for version B 0.89, which is relatively high.[15]

Satisfaction with the therapy (DTSQ)

The DTSQ was developed for measuring satisfaction with the current therapy, and is suitable for people with diabetes type 1 and 2. The questionnaire was developed by Bradly in collaboration with the Diabetes Research Group in 1993.[16,17] The questionnaire consists of eight items and covers three subscales. The scale for this score ranges from 0 (very unsatisfied) to 6 (very satisfied). Two items give an indication of the frequency of hyperglycaemia and hypoglycaemia, the scale for this score ranges from 0 (never) to 6 (often). Hyperglycaemia was defined as a blood glucose value of more than 15.0 mmol/l. A severe hypoglycaemic event was defined as a blood glucose value for which third party assistance was necessary. The internal consistency of this questionnaire was 0.89, which is relatively high.[16,17]

Well-being questionnaire

The questionnaire concerning well-being was originally developed in 1982 to provide an instrument to measure depression, anxiety and the various aspects of well-being. This questionnaire is used by the WHO for measuring new treatment modalities in control of diabetes. The current questionnaire consists of 22 items and four subscales: depression, anxiety, energy and positive well-being. A total

Hoogma, et al. Quality of life and metabolic control in patients with diabetes mellitus type 1.

NOVEMBER 2004, VOL. 62, NO. 10

384

score of general well-being will be obtained by counting the scores after inverting the subscales of depression and anxiety. A four-point scale is used, from 0 (never) to 3 (always). A higher score is consistent with the mental state described by the different subscales. The internal consistency of the subscales has been shown to be sufficient (0.46 to 0.89).[15]

To analyse the difference in quality of life in patients with diabetes mellitus who received a different type of intensive insulin treatment, patients on CSII treatment were compared with patients on MDII. Both groups were given the same questionnaires. Because of the cross-sectional design of the study, statistical analysis was performed by χ^2 for sociodemographic and medical results. All other results were tested by Student's t-test using the SPSS programme. A p value below 0.05 was considered to be statistically significant.

RESULTS

The patient population consisted of 55 patients on CSII who fulfilled the inclusion criteria. Of this group, 49 patients filled in the questionnaire, while six patients were not willing to participate in the trial. A randomly assigned group of 79 patients with MDII coming from the same outpatient clinics formed the control group. Social and demographic data are given in *table 1*. The frequency of self-measurement of blood glucose in the group treated with CSII was once

daily in 81%, five to six times a week in 2%, three to four times a week in 2%, one to two times a week in 10% and never or seldom in 2%. In the MDII group these results were 63, 8, 6, 19 and 4%, respectively. The frequency of performing a full daily glucose profile in patients treated with CSII was 18%, consisting of the measurement of blood glucose four times or more in 63%, three times in 6%, twice in 12%, and once a day in 6%. In the MDII group, 8% of the patients performed a daily glucose profile: 43% four times or more, 11% three times, 25% twice and 8% once a day. In general, patients on CSII performed significantly more controls than the patients on MDII. The number of hypoglycaemic episodes that could be managed by the patient him/herself in the week and in two months before the questionnaire was filled in (*table 2*). No statistical differences were found between the two groups. The HbA_{1c} for the CSII group was 8.1 ± 1.5% and for the MDII group 8.5 ± 1.4%. Only the frequency of blood glucose control was statistically different between the two groups (p<0.05) (*table 2*). No difference was found regarding the outcome of the DQOL measurement between the two groups (*table 3*). Also the satisfaction of treatment measurement, in particular related to hyperglycaemias and hypoglycaemias, did not show any difference (*table 4*).

With regard to general well-being, the group treated with MDII only showed somewhat better results for the subscale 'energy' compared with the group treated with CSII. Regarding the other items there were no statistical differences between the two groups (*table 5*).

Table 1
Social and demographic data

	CSII	MDII
Number of patients	49	79
Sex (m/f) (n)	13/36	43/36
Age (years)	41.4 ± 11.3	43.1 ± 14.8
Marital status		
Married or living together (n)	40	55
Unmarried (n)	7	18
Divorced/widow (n)	2	6
Education (%)		
None	8	5
Low vocational	25	20
Low	8	16
Middle	37	11
Middle vocational	12	18
High	10	27
Unknown	0	3
Duration of diabetes (%)		
>10 years	65	73
5-10 years	29	14
2-5 years	6	10
<2 years	0	3
Retinopathy (%)	2	3
Nephropathy (%)	0.5	1
Smoking (%)	25	22

Table 2
Frequency of self-control, hyperglycaemias and hypogly-caemias

	CSII (%)	MDII
Daily blood glucose control*	81	63
5-6 times/week	2	8
3-4 times/week	4	6
1-2 times/week	10	19
Never or seldom	2	4
Non-serious hypoglycaemia last week (%)		
None	37	35
1	6	25
2-3	43	27
>4	14	9
Hypoglycaemia during the night (%)		
None	63	60
1	21	30
2	16	6
3	0	2
Not available	0	2
Severe hypoglycaemia last 2 months (%)	80	90
Never	16	6
Ones	2	3
Twice	2	0
3 times	0	0
4 times	0	1
HbA_{1c}	8.1 ± 1.5	8.5 ± 1.4

p<0.05 (regarding the number of daily controls).

Hoogma, et al. Quality of life and metabolic control in patients with diabetes mellitus type 1.

Table 3
Results for to the subscales satisfaction, impact, diabetes and general related worries and the total DQOL score

QUALITY OF LIFE	CSII	MDII	P
Satisfaction	4.0 ± 0.6	4.0 ± 0.4	NS
Impact	4.0 ± 0.3	4.1 ± 0.3	NS
Diabetic worries	4.2 ± 0.3	4.2 ± 0.4	NS
Social worries A	4.7 ± 0.3	4.6 ± 0.4	NS
Social worries B	4.5 ± 0.5	4.6 ± 0.3	NS
DQOL A	4.3 ± 0.2	4.2 ± 0.3	NS
DQOL B	4.2 ± 0.2	4.3 ± 0.3	NS

Values are expressed as mean ± SD.

Table 4
Results satisfaction regarding mentioned hyperglycaemias (range 0-6) and hypoglycaemias (range 0-6) and DTSQ total (range 0-6)

DTSQ	CSII	MDII	P
Hyperglycaemia	2.8 ± 1.6	2.7 ± 1.6	NS
Hypoglycaemia	3.5 ± 1.7	3.1 ± 1.7	NS
Satisfaction total	5.1 ± 0.7	5.2 ± 0.7	NS

Values are expressed as mean ± SD.

Table 5
Results for subscales depression (range 0-3), anxiety (range 0-9), energy (range 0-12) and positive well-being (range 0-18) and total well-being (range 0-66)

WELL-BEING	CSII	MDII	P
Depression	3.7 ± 2.6	3.2 ± 2.2	NS
Anxiousness	4.5 ± 3.7	4.0 ± 3.2	NS
Energy	7.5 ± 2.4	8.7 ± 2.3	0.009
Positive well-being	13.2 ± 3.0	13.5 ± 2.8	NS
Well-being total	48.6 ± 9.2	51.0 ± 8.7	NS

Values are expressed as mean ± SD.

CONCLUSIONS

This study shows that patients treated with CSII have similar scores on quality of life scales and respond similarly to questionnaires regarding satisfaction with the treatment and general well-being in comparison with patients treated with MDII. Although we do not know why the patients chose CSII, the CSII group did not differ from the MDII group in duration of diabetes, frequency of complications, marital status and level of education. No statistical difference between the CSII and MDII groups regarding their HBA_{1C} values or the number of severe hypoglycaemias could be detected, although there was a tendency for a better HBA_{1C}

for the group treated with the insulin pump, as has also been shown by the two recent meta-analyses.[3,14] The similar quality of life of patients receiving CSII to those on MDII is in line with previous studies, one of which even showed that the quality of life in patients on CSII had improved.[6] Even the fact that most of the patients who were on CSII therapy had a higher frequency of blood glucose control does not seem to interfere with their quality of life. Based on these results, it may be concluded that the idea some diabetologists seem to have about the impact of CSII therapy as an impairment in quality of life is actually a misconception. One of the main advantages of insulin pump treatment is the provision of a better basal insulin administration instead of the problematic pharmacokinetics and pharmacodynamics of intermittent insulin in case of MDII.[18,19] It may, in fact, be considered as remarkable that patients are capable of regulating their diabetes with these schedules. Also the possibility to temporarily change the basal insulin requirement during different activities in patients with CSII might be considered as at least a theoretical benefit of this treatment strategy and should cause less hypoglycaemias and hyperglycaemias.[18,19] Our study may have been too small to detect such differences. Nevertheless, the results of the group treated with CSII therapy (and those on MDII) might have been better if the patients had been treated with insulin analogues, such as lispro or aspart. In various studies insulin lispro and aspart were shown to result in a slightly better HbA_{1C} without causing an increased incidence of hypoglycaemias.[7,8,20-22]

This study, which is a cross-sectional study, has some limitations. The groups were not randomly assigned; the reasons for choosing CSII therapy were mainly caused by motivation of the patients, the Dawn phenomenon, badly controlled diabetes, and also problems related to the NPH insulin. Because of these reasons the groups are strictly speaking not comparable, although one can argue to what extent these differences could have an effect on the parameters evaluated in this study. Despite these limitations, our data suggest that patients who are in less than optimal control on MDII may be safely offered a trial of CSII therapy.

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Hoogma, et al. Quality of life and metabolic control in patients with diabetes mellitus type 1.

NOVEMBER 2004, VOL. 62, NO. 10

386

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Hoogma, et al. Quality of life and metabolic control in patients with diabetes mellitus type 1.

A 48-year-old woman with abdominal pain and fever

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CASE REPORT

A 48-year-old woman was admitted to our hospital because of abdominal pain and fever. She had had no complaints until three weeks previously, when she experienced progressive weakness and weight loss. Four days before admission she complained of continuous abdominal pain in the left upper and lower quadrant with radiation to the back, accompanied by nausea and fever. There was no history of irregular bowel functions, pyrosis, diarrhoea or dysuria. There where no previous hospital admissions and she was not taking any medication, accept occasionally acetaminophen during the last few days. Physical examination revealed a temperature of 39°C, the pulse was 110 beats/min and blood pressure 130/80 mmHg. She also appeared pale. The abdomen was soft but tender especially in the left lower quadrant, without guarding. A rectal examination was unremarkable. Laboratory results were as followed: haemoglobin 6.7 mmol/l, leucocytes 25.8 x 10^9/l, C-reactive protein 451 mg/l, alkaline phosphatase 236 U/l, γ-glutamyltransferase 86 U/l, glutamic-pyruvic transaminase 44 U/l, glutamic-oxaloacetic transaminase 29 U/l, amylase 33 U/l and lactate dehydrogenase 377 U/l.
Computed tomography of the abdomen is shown below.

WHAT IS YOUR DIFFERENTIAL DIAGNOSIS?
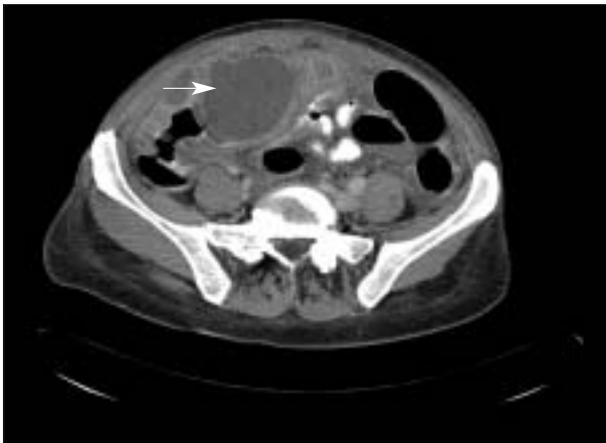
Figure 1
Computed tomography shows a large abdominal mass in the right lower abdomen (see arrow)

Figure 2
Computed tomography shows an intrauterine device in situ (see arrow)

CASE REPORT
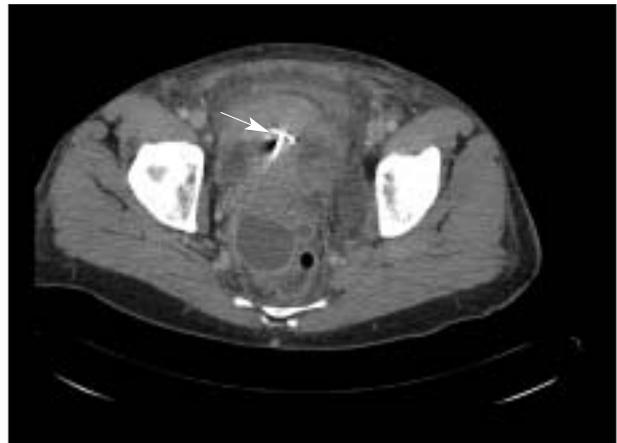
Retroperitoneal fibrosis caused by pergolide in a patient with Parkinson's disease

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ABSTRACT

Retroperitoneal fibrosis (RPF) is an uncommon disorder that may cause ureteric obstruction with renal damage. Pergolide, a dopaminergic agonist used in the treatment of Parkinson's disease, has rarely been related to the development of RPF. We report on a 78-year-old woman with Parkinson's disease who presented with hydroureteronephrosis and developed RPF and serosal fibrosis during treatment with pergolide. Following discontinuation of pergolide therapy and placement of a double-J stent, her renal function improved. Inflammatory markers returned to normal limits within two months and the retroperitoneal fibrotic mass became smaller.

INTRODUCTION

Retroperitoneal fibrosis (RPF) is a rare disease which may result in obstructive uropathy and renal failure. The disease may be idiopathic or secondary. More than two thirds of patients with RPF have idiopathic RPF.[1,2] RPF associated with drugs and has been especially described with the ergot derivatives methysergide and bromocriptine.[3,4] Pergolide is also an ergot derivative dopaminergic agonist commonly used in the treatment of Parkinson's disease (PD).[5] RPF secondary to pergolide is very rare, but has previously been reported.[6-10] We describe a case of RPF associated with pergolide use in a patient with PD and have reviewed literature.

CASE REPORT

A 78-year-old woman, who was found to have Parkinson's disease in 1990 at the age of 65, was initially treated with levodopa/benserazide (50/12.5 mg orally, three times a day). Bromocriptine was added in 1991 and selegiline in 1993 because of increasing parkinsonian symptoms. Her symptoms worsened and tremor increased under this treatment. A stereotaxic neurosurgical intervention was performed to the thalamus and pergolide treatment was started in 1999; bromocriptine and selegiline were stopped while levodopa/benserazide was continued. With pergolide therapy, her parkinsonian symptoms improved and the pergolide was increased gradually to 3 mg/day.

She had a history of hypertension, which had been well controlled for two years with amlodipine 5 mg/day orally. Four months ago, swelling and erythema of her left leg developed and was treated with warfarin 5 mg/day orally for deep venous thrombosis, but treatment was stopped within five days because of diffuse ecchymoses. Doppler ultrasonography was not undertaken. Her swelling and erythema decreased spontaneously. She was then admitted with complaints of low back pain, pretibial oedema, nausea, vomiting and anorexia which had started two months ago. High titres of serum blood urea nitrogen (BUN) and creatinine were detected in biochemical testing and urinary ultrasonography revealed bilateral hydroureteronephrosis. With these findings she was transferred to our hospital. On examination, she was pale, her blood pressure was 130/80 mmHg, with a pulse of 88 beats/min and her heart sounds and jugular venous pressure were normal. There was a 2/6 systolic murmur at the apex. Her breathing sounds were normal except for mildly decreased sounds in the lower zones of both lungs. No organomegaly or

lymphadenomegaly was found. She was afebrile and had mild pretibial oedema. There were signs of Parkinson's disease on neurological examination.

The results of her initial laboratory examination were as follows: BUN 14.4 mmol/l, creatinine 250 μmol/l, glucose normal, sodium 143 mmol/l, potassium 5.1 mmol/l, uric acid 0.25 mmol/l, ALT 20 IU/l, AST 33 IU/l, LDH 526 IU/l, alkaline phosphatase 214 IU/l, total protein 7.6 g/l, albumin 3.6 g/l, erythrocyte sedimentation rate (ESR) 94 mm/h, C-reactive protein (CRP) 37.6 mg/l, total bilirubin normal, total cholesterol 3.9 mmol/l, triglyceride 0.73 mmol/l, intact parathyroid hormone 60.6 pg/ml (12-72), white blood cell 5.9 x 10^9/l, haematocrit (Hct) 0.29 l/l, platelets 285 x 10^9/l, iron 10.4 μmol/l, total iron binding capacity 45.4 μmol/l and ferritin 601.5 ng/ml. Urine analysis revealed a urine density of 1012, protein negative, pH 5, three erythrocytes and 13 leucocytes per high-power field. The daily urine volume was approximately 1200 ml. Glomerular filtration rate (GFR) was 8.8 ml/min. Hepatitis B and C serology, and anti-HIV were negative.

Chest X-ray showed bilateral mild pleural effusion in the lower zones of lungs and electrocardiography was normal except for incomplete left bundle branch block. Computed tomography (CT) of the thorax revealed minimal bilateral pleural effusion, thickening of pleura and mild pericardial effusion. Echocardiography suggested 50% ejection fraction, minimal pericardial effusion and mild thickening of pericardium. Because of a pleural effusion, thoracentesis was performed. The results of the pleural fluid proved to be exudate. Bacteria and acid-fast bacilli were not detected, and polymerase chain reaction assay for tuberculosis was negative. Fluid culture was also negative. Cytopathological examination of pleural fluid showed no malignant cells, but there were some fibroblasts. Pleural biopsy could not be performed due to minimal pleural effusion. Abdomen and pelvic CT scans revealed bilateral hydroureteronephrosis, a presacral soft tissue mass measuring 2 cm at the widest location and extending bilaterally to the pelvic wall. Based on these findings, bilateral double-J stents were inserted; BUN and creatinine decreased gradually and her symptoms improved. Pelvic magnetic resonance imaging (MRI) showed presacral mature and immature fibrotic tissue which was hypointense in T_2 weighted and hyperintense in T_1 weighted images, and that measured 1.7 cm at the widest location (*figure 1*). This tissue extended to the 5th lumber spine vertebrae. A diagnosis of RPF was made. A true-cut biopsy was carried out for excluding malignancy. Histopathological examination revealed no evidence of malignancy, but fibroadipose tissue was seen. After exclusion of other possible causes, RPF was attributed to pergolide therapy and the pergolide was discontinued. Pericardial and pleural thickening were thought to be associated with fibrosis due to pergolide. MRI angiography was planned for detecting a possible constriction of a major vessel,

but was not performed due to the hazardous effect of the contrast agent on renal function. Doppler ultrasonography of the lower extremities revealed no thrombi. Two months later, control pelvic MRI showed reduction in fibrotic tissue that now measured 1.1 cm (*figure 2*), serum ESR and CRP levels had decreased and GFR increased to 27 ml/min. Because of her age and the risk of osteoporosis, we decided not to treat with corticosteroids or immunosuppressive drugs. After a follow-up of four months, the patient's ESR was 30 mm/h, CRP was 3.1 mg/l, BUN 11.5 mmol/l and creatinine were 120 μmol/l.

DISCUSSION

An aetiology of RPF is detected in only about one third of the patients. Secondary causes of RPF include drugs such as ergot derivatives, infections (such as HIV or tuberculosis),

Figure 1
Sagital T_2 weighted MRI images depict a presacral soft tissue of heterogenous intensity
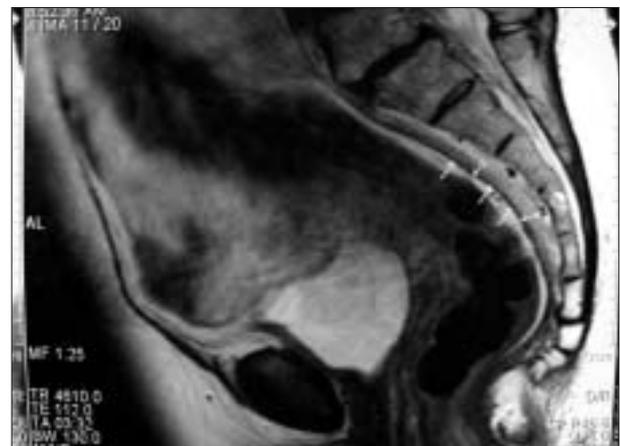
Figure 2
Two months later control MRI examination showed that the soft tissue had regressed in size

Bilici, et al. Retroperitoneal fibrosis caused by pergolide.

NOVEMBER 2004, VOL. 62, NO. 10

390

haemorrhage, malignancy and aortic aneurysm.[1,2,11,12] Associations with connective tissue diseases, including ankylosing spondylitis, systemic lupus erythematosus, polyarteritis nodosa and Wegener granulomatosis have been previously reported. In addition, HLA-B27 may be positive in some cases.[12-14] In our patient ANA and HLA-B27 were negative and anticardiolipin antibodies were within the normal range. Laboratory results showed elevated ESR and CRP and normochromic normocytic anaemia. An elevated ESR has been reported in 80 to 90% of cases of RPF.[2,8,12,15] Therefore, ESR and CRP may be used for follow-up of such patients. The best diagnostic tests for RPF are imaging methods. CT is the most frequently used method. Although MRI provides separation of RPF from muscle or adipose tissue compared with CT, its superiority has not been established.[16,17] We made the diagnosis of RPF based on CT and MRI findings. A biopsy was then performed and RPF diagnosis was confirmed by histopathological findings. The necessity of laparoscopic or open biopsies has been emphasised to exclude malignancy and establish other causes of secondary RPF by some authors.[2,12] On the other hand, malignant areas may be missed with both laparoscopic and open biopsy. Either CT or ultrasonographic-guided percutaneous needle biopsy should be carried out in each case of diagnostic doubt[2,12] to exclude malignancy, infection and other causes of secondary RPF. Our patient had had Parkinson's disease for 13 years and she had been taking pergolide since 1999. Pergolide is a dopaminergic agonist and RPF associated with this drug has been previously recognised in five cases according to the English medical literature (*table 1*).[6-10] Pergolide-induced RPF is the most probable diagnosis in our patient because of lack of other secondary causes. Although in the five other reported cases, the RPF had a typical location, our case involved the presacral region, an atypical site. RPF typically involves soft tissue mass, surrounding the ureters, kidney and vascular structure.[11,12] Pergolide-induced RPF usually occurs on average two years after the initiation of pergolide.[8,10] In our patient, initial symptoms started in the fourth year of treatment. Pergolide therapy was discontinued in all reported patients. Only one patient (case 1) was treated with corticosteroids. Ureteric stents were inserted in four of the cases. In addition, two patients (cases 2 and 3) were treated surgically. The clinical features and management of pergolide-induced RPF patients are summarised in *table 1*. Serosal fibrosis related to pergolide has been documented,[8,18] but in these cases, serosal fibrosis and RPF occurred separately. Further, we detected a simultaneous occurrence of pleural and pericardial fibrosis and RPF in our patient. The mechanism of RPF caused by ergot derivatives, such as bromocriptine and pergolide, is not entirely understood, but an idiosyncratic immune response associated with the drug, which acts as a hapten, is considered to be the causative mechanism of RPF. In addition, mononuclear cell infiltrations have been reported in biopsy specimens.[19] However, the mechanism of RPF associated with methysergide differs from the other ergot alkaloids. Methysergide behaves as a serotonin antagonist and a prolonged intake of this drug causes rebound release of serotonin. There is a profibrotic effect of serotonin and this might be responsible for the development of RPF.[12,20] Because of these findings, corticosteroids are effectively used for suppressing the inflammation, especially in the early stages.[2,11,14] The trials of other treatment modalities

Table 1

The clinical features and management of pergolide-induced RPF patients

CASE	AGE/SEX	TIME INTERVAL*	LOCATION	SEVERITY OF DISEASE	OTHER MANIFESTATIONS OF FIBROSIS	TREATMENT**	RESPONSE TO TREATMENT	REFERENCE
1	61/M	24 months	Typical	Mild RF, left H, EE	-	Corticosteroid 20 mg/day	Successful	8
2	68/F	24 months	Typical	Severe RF, bilateral H, anaemia	-	Ureterolysis and omental wrap	Successful	7
3	68/F	28 months	Typical	Severe RF, left H, EE	-	Surgical removal of mass, US	Successful	6
4	83/F	19 months	Typical	Severe RF, bilateral H	-	US	Successful	10
5	63/F	21 months	Typical	Severe RF, bilateral H, anaemia	-	Nephrostomy, US	Successful	9
6	78/F	48 months	Atypical	Mild RF, bilateral H, EE, anaemia	Pericardial and pleural fibrosis	US	Successful	This report

*Time interval between the start of pergolide and development of symptoms and/or the diagnosis of RPF, **Pergolide was discontinued in all patients.
RF = renal failure, H = hydronephrosis/hydroureteronephrosis, EE = elevated erythrocyt sedimentation rate, US = ureteric stent.

Bilici, et al. Retroperitoneal fibrosis caused by pergolide.

in RPF such surgery, tamoxifen and immunosuppressive drugs have been documented in some cases.[21,22] After pergolide therapy was discontinued, the pelvic MRI showed a reduction in the fibrotic mass, and serum ESR and CRP decreased. Therefore, she was left untreated and a follow-up was decided.

This patient is a rare case of RPF and possible pleural-pericardial fibrosis caused by pergolide. In patients with Parkinson's disease who receive pergolide, renal function, ESR and CRP levels should be closely checked. RPF should particularly be considered in the differential diagnosis of elevated ESR, CRP and disturbance of renal function in patients with Parkinson's disease treated with pergolide. ESR and CRP levels are important for both diagnosis and response to treatment in these patients.

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Stopper CARDS III

Bilici, et al. Retroperitoneal fibrosis caused by pergolide.

Pituitary apoplexy presenting during pregnancy

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ABSTRACT

Pituitary apoplexy during pregnancy is a rare but serious event with significant morbidity and even possible mortality if not recognised in time. A 26-year-old woman was admitted with sudden onset of severe headache, vomiting, disturbed consciousness and photophobia. MRI showed a pituitary apoplexy. Adrenal insufficiency with circulatory shock was present together with deficiency of the other hormones produced by the adenohypophysis. After treatment with glucocorticoids, diabetes insipidus developed for which treatment was given. She was treated conservatively and the clinical picture improved in a few days, followed by an uneventful pregnancy and delivery. A second MRI showed regression of mass effect with tumour expanding into the left cavernous sinus. No signs of tumour progression or abnormal hormone secretion have occurred up to one year after the event. Complete pituitary insufficiency has remained. The literature on the subject is reviewed with special emphasis on the circumstances in which pituitary apoplexy occurred and on the treatment of this endocrine emergency.

In conclusion, pituitary apoplexy is a rare complication of pregnancy. The severe consequences of missing the diagnosis underline the importance of this potentially lethal endocrine emergency.

INTRODUCTION

Pituitary apoplexy is a clinical syndrome consisting of sudden onset of severe headache, altered consciousness, vomiting, visual disturbances and ophthalmoplegia. It is caused by haemorrhage and/or infarction in the pituitary gland. Usually a pre-existing pituitary adenoma is present but it has also occurred in lymphocytic hypophysitis. Pituitary apoplexy has been associated with various conditions. The occurrence during pregnancy is rare and there have only been a few reports in the literature.

In this case report we present a woman who developed pituitary apoplexy during pregnancy as the first manifestation of a pituitary adenoma.

CASE REPORT

A 26-year-old woman was admitted to the gynaecological ward because of severe headache and nausea in the 23rd week of her second pregnancy. Her first pregnancy had been uneventful, as had her second up to three days before admission. Before the onset of this pregnancy she reported nine months of amenorrhoea. On admission she complained of a sudden onset of severe continuous headache radiating to the neck accompanied by nausea, vomiting and photophobia.

On physical examination, lowered consciousness and extreme photophobia were present. There were no signs of meningismus. Visual acuity could not be determined because of the photophobia. Diplopia was present on lateral gaze in both directions. No signs of other cranial nerve dysfunction were noticed. Fundoscopy showed papilloedema. Laboratory results for haematology were normal and CRP was slightly elevated at 10 mg/l (normal <3). Serum sodium was severely lowered (107 mmol/l, normal 136 to 146).

Potassium concentration was slightly decreased (3.4 mmol/l, normal 3.8 to 5.0), probably due to the vomiting and serum creatinine was normal (30 μmol/l, normal <110). Urine sodium concentration was low (3 mmol/l).

The consulting neurologist's most probable diagnosis was a sagittal sinus thrombosis and an MRI scan combined with MRA was performed. No signs of thrombosis were present, however a 2 cm large pituitary tumour was seen (*figures 1a* and *b*). On the T_1 weighted image the signal intensity was high and on T_2 low, compatible with haemorrhage in a pituitary mass.

When first seen by the endocrinologist she was in shock and after blood was drawn 100 mg of hydrocortisone was given directly intravenously, followed by a constant infusion of 200 mg per 24 hour. Intravenous fluid expansion was given to restore adequate circulation in the next hour followed by infusion of a 0.9% sodium-chloride solution. Subsequently polyuria developed for which treatment with desmopressin was initiated.

Laboratory results before hydrocortisone were as follows: cortisol 0.69 μmol/l, prolactin 912 mU/l (normal 70 to 500), FT_4 5.9 pmol/l (normal 11 to 24), IGF-I 4.9 nmol/l (normal 10 to 45). In the next few days the patient developed temporary paresis of both fourth cranial nerves followed by complete recovery of all ocular pareses. Clinical improvement continued in the following days and after suppletion of hydrocortisone, thyroxin and desmopressin, the pregnancy developed uneventfully. A new MRI eight weeks later showed regression of the pituitary mass with signs of invasion of the left cavernous sinus, comparable with a pre-existing pituitary tumour. Delivery after 38 weeks of pregnancy was uneventful and a healthy son was born. One year after the event no signs of pituitary tumour growth or hormone overproduction are present, although panhypopituitarism remains.

DISCUSSION

Pituitary apoplexy, first described by Baily in 1898, is an endocrine emergency with significant morbidity and mortality if not recognised in time.[1] The incidence in surgical series of pituitary tumours is somewhere between 0.5 and 10%.[2-5] In 80% of cases, pituitary apoplexy is the presenting symptom of a pituitary adenoma, as in our patient.[4,5] It is thought to be caused by either infarction, haemorrhage or possibly both in the pituitary; however the pathophysiology remains unknown.[6,7] Asymptomatic necrosis and/or haemorrhage occurs more often and is found in up to 28% of pathologically examined pituitary adenomas.[2] Pituitary apoplexy has been associated with several conditions, such

Figure 1A
Coronal T1-weighted image of the pituitary gland
White arrow: optic chiasm, short arrow: pituitary gland, broken arrow: internal carotitid artery.

Figure 1B
Saggital T1-weighted image of the pituitary gland
White arrow: haemorrhagic part of pituitary gland, broken arrow: enlarged pituitary mass, short arrow: pituitary stalk.

as hypertension, dynamic testing of pituitary function, use of GnRH analogue, bromocriptine, anticoagulants and general anesthesia.[4,8-16] Pituitary apoplexy during pregnancy is very rare. We found only seven cases in the literature: three were macroprolactinomas, two growth hormone-secreting adenomas, one was nonsecretory and no information was presented in one case.[17-23] *Table 1* shows the presenting symptoms and signs, treatment and outcome. In retrospect, no clinical signs of hormone overproduction were present in our patient at the event and during her follow-up no signs of a hormonally active adenoma were measured or observed either.

De Heide, et al. Pituitary apoplexy presenting during pregnancy.

NOVEMBER 2004, VOL. 62, NO. 10

394

In pregnancy, especially in the third trimester the clinical picture of pituitary apoplexy shows considerable resemblance to lymphocytic hypophysitis. Both can present as a suprasellar mass on magnetic resonance imaging. On T_1 weighted images they can be differentiated as haemorrhage usually shows hyperintensity and hypophysitis is classically hypointense compared with the rest of the brain.[24] Pituitary apoplexy in a case of lymphocytic hypophysitis during pregnancy has also been reported.[25] Our patient's most likely underlying disease is a pituitary adenoma as on follow-up MRI there is clear invasion of the cavernous sinus.

Although cavernous sinus invasion has been reported in lymphocytic hypophysitis this has only occurred in males thus far.[2] The normal pituitary gland increases in size during pregnancy with a total increase of 3 mm at the end of pregnancy. The existing adenoma in our patient together with the normal increase in the pituitary gland during the pregnancy could have compromised the blood supply too, either leading to infarction or haemorrhage. Oestrogens in an experimental animal model cause hyperaemia of the hypophysis and could therefore contribute to the risk of pituitary apoplexy in pregnancy.[27] Treatment of pituitary apoplexy consists of replacement of the deficient hormones, especially glucocorticoids, close surveillance and transsphenoidal surgery. Some advocate conservative management except if no spontaneous improvement or worsening of visual impairment and/or consciousness occurs.[28] Others prefer direct surgery, preferably within the first eight days after the event, claiming that this intervention improves outcome regarding both visual impairment and pituitary function.[5,29] No clinical trials comparing these two treatment strategies have been carried out so far. Although transsphenoidal surgery during pregnancy is safe, we chose conservative management in our patient as rapid clinical improvement followed treatment with glucocorticoids and desmopressin. Whether pituitary function could have been saved by early surgery in our patient remains unknown.

In conclusion we present a rare complication of a pituitary tumour during pregnancy with severe consequences underlining the importance of the diagnosis pituitary apoplexy.

ACKNOWLEDGEMENT

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Table 1

Signs, symptoms, treatment and outcome in six cases of pituitary apoplexy presenting during pregnancy as reported in the literature

REFERENCE	FUNCTIONALITY TUMOUR	SIGNS/SYMPTOMS	TREATMENT	OUTCOME
17	Prolactinoma	Headache, vomiting, left abducens paresis, fatigue	Hydrocortisone, thyroxin	Uneventful pregnancy, complete recovery
18	Prolactinoma	Headache, left-sided ptosis, coma	Left frontal craniotomy, bromocryptine	Left-sided third cranial nerve palsy
19	Growth hormone	Headache, bitemporal hemianopsia, decreased visual acuity	Transsphenoidal decompression	Complete recovery of vision and visual fields
20	Growth hormone	Headache, vomiting, blurred vision	Transsphenoidal decompression	Complete recovery
22	Prolactinoma	Headache, hemianopsia, left-sided opthalmoplegia	Transsphenoidal decompression	Complete recovery
23	Nonsecretory	Headache, bitemporal hemianopsia	Transsphenoidal decompression	Minimal diplopia

No data were available for reference 21.

De Heide, et al. Pituitary apoplexy presenting during pregnancy.

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De Heide, et al. Pituitary apoplexy presenting during pregnancy.

NOVEMBER 2004, VOL. 62, NO. 10

396

The structure of medical competence and results of an OSCE

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ABSTRACT

Background: Medical competence is a central concept in medical education. Educational efforts in medical training are directed at the achievement of a maximal medical competence. The concept of the structure of medical competence (multidimensional or one-dimensional with strongly interrelated competences) therefore affects the educational developments and assessment procedures.

Purpose: To examine the applicability of a one or more dimensional character of medical competence in student assessments, by analysing the results of 356 students in the history taking station of an objective structured clinical examination (OSCE), in relation to other assessment procedures.

Methods: The performances of 356 students in a history taking station of an OSCE were analysed. Analyses of the checklist scores were aimed at the dimensionality of history taking skills. External criteria were used to test the validity of the scores on the checklist.

Results: The analyses of the scores on the history taking checklist indicated at least five dimensions of history taking skills: the frequency of patient-centred skills, the quality of performance of patient-centred skills, complaint-oriented skills, general social skills, and the provision of procedural information.

Conclusion: Medical competence, as a subject of assessment, can be seen as a multifaceted construct. This study shows that history taking alone might be composed of five different dimensions, suggesting that medical competence in respect of assessment might be viewed as a multifaceted construct which in that sense has implications for the assessment of medical competence.

INTRODUCTION

Medical competence is a central concept in medical education. Most of the educational efforts in medical training seek to accomplish a growing medical competence of the students, eventually to such a level that they can take up medical practice independently. But although it is one of the central elements in medical education there is no agreement as to what its structure should be. Some[1-4] see it as multidimensional, encompassing distinct competences, others[5-8] consider it to be a one-dimensional construct containing strongly interrelated competences that can hardly be separated. At present, opinion tends to treat medical competence as a complex of knowledge, skills, emotions, values and habits, most of which are seen as strongly interrelated.[9] An example of medical competence viewed as a multidimensional assessment entity is that of Metz,[1] introduced in 1984. This model of medical competence was constructed on the basis of four separate skills: perceptive, intellectual, motor, and social skills. In this model, *perceptive skills* are defined as the abilities to discern and interpret by perceptive means, various elements indicative of diseases. Central in *intellectual skills* is cognitive functions, more precisely not just the theoretical knowledge itself, but its application, for example knowing the right questions when taking a history. *Motor skills* indicate the ability to conduct

the appropriate manual procedures in medical examinations. *Social skills* refer to communication and interactions both with patients and with other healthcare professionals. One of the important advantages of this four-dimensional model is that it very adequately enables the construction of assessment procedures because the observations and scores can be based on these four different skills. In this way the judgement of the achievements of the students and the formative feedback could be more detailed.

In 1985, Norman[2] undertook a methodological review of the models of competence that were then available. He concluded that at that point no single model could adequately define the prerequisite knowledge, skills and attitudes required for a competent physician. Therefore, he introduced the categorisation of clinical competence in clinical and technical skills, knowledge and understanding, interpersonal attributes and capabilities in problem-solving and clinical judgement. So, taking these together, medical competence can be thought of as a multifaceted construct whereby the various contributing elements are interdependent and overlapping and should be assessed as such.[1,2]
At present there are indications that medical competence could be assessed by using global ratings, as these would be as reliable and valid as more comprehensive checklists.[10] Although this might be true in general for giving an overall impression of a certain clinical skill, the question remains whether such a global rating is precise enough to detect shortcomings in the learners sufficiently to warrant precise feedback, corrections or educational changes. So, for purposes of assessment, it is of great importance to obtain more insight into the question whether medical competence should be seen as being a one-dimensional entity and tested as such, or as a more dimensional model, built up of multiple recognisable elements and justified in testing developing medical competence of students.
The aim of this study was to examine if a one or more dimensional character of medical competence could be uncovered in the assessment of medical competence of undergraduate medical students. If analysis of the results were to point towards one dimension, this would support the validity of the one-dimensional construct in medical competence testing. But if more dimensions can be discerned in history taking skills, a 'multifaceted' model of medical competence testing would seem more appropriate and global ratings would not seem detailed enough to cover the assessment of competence.

METHODS

Participants
The results of 356 students (160 male (45%) and 196 female (55%) students) at the history taking station of an objective

structured clinical examination (OSCE) were analysed. The students participated in the OSCE of the practical clinical training module 1, just before the start of their clerkships, in the fifth year of their study. (In the Netherlands the medical undergraduate curriculum usually contains four years of mainly preclinical education, followed by two years of mainly clerkships).

Description of the OSCE
The OSCE consists of twelve stations with five minutes for each station. A distinction was made between process- and product-centred stations: trained expert-observers observed three process-centred stations (one of which a history taking station) with checklists, while the results of nine product stations (for example interpretation of ECG) were rated on the final product. The OSCE was based on the four skills (perceptive, intellectual, motor and social) of Metz's model of medical competence.

Procedure
In five minutes, students completed part of a history taking of one of the standardised patients. Four standardised patients carefully trained for their roles participated in this study. The validity of simulated patients has been demonstrated before.[11] Two expert-observers were trained in the use of the history taking checklist. Their training started with an explanation of the content of the items, followed by a hands-on training with video material. The training aimed to accomplish a 90% agreement in scoring behaviour that was obtained in two half-day sessions.[12] Every four weeks one of the two observers participated in the OSCE, mostly real time by a one-way screen, sometimes from a videotape.

The checklist
The history taking checklist consisted of 24 items: 8 were directed at social skills and 16 addressed intellectual skills. These intellectual skills, especially items 15 to 19, focussed on the medical content in a general way. They are directed at the achievements of the students to gather medical information irrespective of case content. Students did not know the content of the list, but the checklist items reflected the goals of the training activities. The construction of the checklist was based on the MAAS-R (Revised Maastricht history taking and advice checklist)[13] that has proved to be a valid instrument in assessing the essential elements in history taking. To guarantee further the content validity of the checklists, the construction was supervised by a steering group of medical experts from different disciplines. The checklist used in this study is directed at the basic communication skills and at the more general elements of medical data gathering, not directly at the medical content of the case histories. In *table 1* the items of the checklist history taking are shown. The items 1, 2, 3, 13, 20, 21, 22 and 24 referred to social skills; the remaining items were aimed

Jacobs, et al. The structure of medical competence and results of an OSCE.

NOVEMBER 2004, VOL. 62, NO. 10

398

Table 1

Checklist 'history taking' with frequency distribution of items

	YES	NO			OPEN
1. Introduction	352	3			1
	GOOD	**MODERATE**	**BAD**		
2. Explanation of position (clerkship, training)	134	192	30		
	YES	**NO**			
3. Proposition of plan	103	253			
	GOOD	**MODERATE**	**BAD**	**NOT SHOWN**	**OPEN**
4. Questions about reasons for encounter	334	22	0	0	
5. Exploration reason for encounter	225	104	20	6	1
6. Questions about expectation of consultation	17	14	2	312	11
7. Questions about presumptions, ideas about complaints	68	18	4	261	5
8. Exploration of impact complaint on daily life	25	20	6	297	8
9. Information about self-help and results	68	35	2	245	6
10. Reaction of social environment on complaint	20	4	0	324	8
11. Patient's activities out of house (resumption of work)	7	3	0	337	9
12. Recapitulation of history so far	144	94	25	92	1
13. Use of common, understandable language	305	46	3	1	1
14. Checking information in recapitulation	143	81	27	102	3
15. Questions about medical history	78	184	29	55	10
16. Getting a clear view of complaint	140	195	20	1	0
17. Questions about period of complaint (origin, development)	198	135	17	3	3
18. Questions about course and duration of present complaint	168	170	16	2	0
19. Questions about noted correlation with other symptoms	70	241	42	3	0
20. Results in relation to complaints and expectations	12	38	7	298	1
21. Checking if reasons for encounter have been discussed	3	8	3	342	0
22. Creation of space for patient to express himself/herself	246	97	12	n.a.	1
23. Proper winding up consultation/making appointments	50	100	32	173	1
24. Showing empathy	188	151	15	n.a.	2

n.a. = not applicable.

at intellectual skills. Response categories on the respective items were 'yes-no' or 'good – moderate – poor – not shown'. To validate the checklist, results of the detailed checklist were compared with the global appreciation of history taking skills by each group's own tutor. The tutor, a medical specialist, supervises a group of 12 students very closely for four weeks during training sessions and coaches them in clinical skills including history taking, together with a psychologist. At the end of this period the tutor gives each student: 1) a global grade for history taking skills, based on the overall performance during the entire four weeks, 2) a grade for medical knowledge and 3) one overall grade.

These grades were used as external criteria in the study. Another external criterion is the mean score of the student in the nine product stations of the OSCE, these stations (for example interpretation of ECG) were scored on their final product and not observed.

Analysis

First, frequency distributions of the items were inspected. Next, factor analyses were conducted to assess the dimensionality of the test scores. Furthermore, correlations of the scores on the history taking checklist with external criteria were calculated to assess the external validity of the scores on the history taking checklist.

RESULTS

Table 1 shows the frequency distributions of the scores on the items of the observation list for history taking. Frequency distributions revealed that for several items the frequencies of the scoring category 'not shown' were quite high (*table 1*). For the items 6 to 11, 20, and 21, the percentage of students who did not pay attention to these items was above 50%. Factor analysis of the scores did not show an interpretable solution (percentages explained variance for the

Jacobs, et al. The structure of medical competence and results of an OSCE.

NOVEMBER 2004, VOL. 62, NO. 10

399

first three factors were 15.04, 10.08 and 7.33% respectively). The reliability of the scores on all 21 items (Cronbach's alpha) was 0.66 with a mean inter-item correlation of 0.10. For the two distinct groups of items, social skills (8 items) and intellectual skills (16 items), the reliability of the scores (Cronbach's alpha) was 0.50 (mean inter-item correlation was 0.13) and 0.58 (mean inter-item correlation was 0.09). The poor scalability of the items may be due to the high frequencies of the category 'not shown'. Because of this, we found it useful to further explore the meaning of the scoring category 'not shown'. The question that we addressed was: is a 'not shown' activity worse than a badly performed activity? Therefore the frequency of performed activities and the relation between the number of performed activities and the level of performance was explored.

Intellectual skills

Because of the content of items 6 to 11, and due to the fact that the observations showed a large number of students not performing these items, we initially focussed on these items, each of which referred to a patient-centred intellectual skill. To further explore the scores on these items, the number of items the students actually performed was counted (range: 0 to 6). The frequency distribution of the number of demonstrated patient-centred items is shown in *table 2*. *Table 2* shows that a total number of 165 students did not show any of the patient-centred intellectual items, and that a total number of 191 students demonstrated one or more of those items. None of the students demonstrated all six items. To address the issue of the relationship between the number of items performed and the level of performance, the mean item score for students who actually demonstrated any item was computed. The mean score of the quality of performance of the 191 students who performed at least one of the items was 2.63 (sd = 0.48).

For the 191 students who demonstrated one or more patient-centred items, the correlation between the number of demonstrated items and the quality of performance was -0.08 (df = 189, p=0.30). This means that there is no rela-

tionship between the number of demonstrated items and the quality of performance. This result implies that the scoring categories 'not shown, poor, moderate, and good' can not be perceived as a one-dimensional interval, or even an ordinal, scale. The number of performed activities does not indicate the level of performed activities. Therefore, the two variables were used separately in further analyses.

For the remaining intellectual items (complaint-oriented items) factor analysis was applied to assess the dimensionality of the item scores. Students who did not perform one of these activities were removed from the analysis. *Table 3* shows the pattern coefficients and communalities of the five intellectual items. A one-dimensional solution explained 33.9% of item variance. Factor analysis revealed one dimension in these complaint-oriented items. This dimension can be labelled as the 'complaint orientation of history taking' (Cronbach's alpha = 0.71).

Social skills

For the presumed remaining social skills, factor analysis was applied to assess the dimensionality of the item scores. Students who did not perform one of these activities were removed from the analysis. *Table 4* shows the pattern coefficients and the communalities of five social skills. A two-dimensional solution explained 48.1% of item variance. Factor analysis showed that two dimensions of skills could be discerned. The first dimension could be labelled 'general social skills' (Cronbach's alpha = 0.61), the second dimension 'providing procedural information to the patient' (abbreviated as: 'procedural information'; Cronbach's alpha = 0.73). Items hardly differentiating between students (items 1, 4, 20, 21) and items which did not, or not enough, relate with other items (items 5, 12, 14, 23) were kept outside the analysis. For each scale, scores were calculated by computing mean scores for items referring to one of the distinguished dimensions. Descriptive statistics of the scales are summarised in *table 5*.

To examine the interconnectedness of scores on these separate scales, correlations between the scale scores were calculated (*table 6*). Except for the correlation between 'complaint orientation' and 'general social skills', correlations between the scales were quite low.

Criterion-related validity of history taking skills

For validation of the identified dimensions in history taking skills, scale scores were correlated with other performance data: 1) the tutor's global appreciation of history taking skills, 2) knowledge estimate by tutor, 3) the overall grade by tutor and 4) the mean score on the product stations of the OSCE (*table 7*). Correlations between these scores were quite low, which means that the scores on history taking skills were weakly related to these external criteria.

Table 2
Frequency distribution of the total number of demonstrated patient-centred intellectual items (items 6 through 11)

VALUE	FREQUENCY	%
0	165	46.4
1	108	30.3
2	51	14.3
3	27	7.6
4	3	0.8
5	2	0.6
6	0	0

Jacobs, et al. The structure of medical competence and results of an OSCE.

NOVEMBER 2004, VOL. 62, NO. 10

400

Table 3

Factor analysis of complaint-oriented items with communalities (h²) and percentage explained item variance (n=286)

	F1	H²
15. Questions about medical history	0.54	0.29
16. Getting a clear view of complaint	0.59	0.35
17. Questions about period of complaint (origin, development)	0.68	0.46
18. Questions about course and duration of present complaint	0.67	0.45
19. Questions about noted correlation with other symptoms	0.38	0.14
		33.9% explained item variance

F1 = complaint orientation of history taking.

Table 4

Factor analysis of social items with communalities (h²) and percentage explained item variance (n=351)

	F1	F2	H²
2. Explanation of position (clerkship, training)	0.14	0.81	0.78
3. Proposition of plan	-0.02	0.77	0.80
13. Use of common, understandable language	0.41	0.06	0.46
22. Leaving room for patient to express himself/herself	0.60	0.06	0.56
24. Showing empathy	0.78	-0.02	0.57
			48.1% explained item variance

F1 = general social skills, F2 = providing procedural information to the patient.

Table 5

Descriptive statistics for five scales of history taking skills

SCALE	N	M	(SD)
Intellectual skills			
Patient-centredness/frequency (items 6-11)	356	0.88	(1.03)
Patient-centredness/quality (items 6-11)	191	2.63	(0.48)
Complaint orientation (items 15-19)	355	2.31	(0.39)
Social skills			
General social skills (items 13, 22, 24)	356	2.64	(0.38)
Procedural information (items 2, 3)	356	1.94	(0.69)

Theoretically, the scores on all scales, except for the scores on patient-centredness/frequency, can range from 1 to 3.

Table 6

Correlations between the five scales of history taking skills

	PATIENT-CENTREDNESS/ FREQUENCY	PATIENT-CENTREDNESS/ QUALITY	COMPLAINT ORIENTATION	GENERAL SOCIAL SKILLS	PROCEDURAL INFORMATION
Intellectual skills					
Patient-centredness/frequency	––				
Patient-centredness/quality	-0.08	––			
Complaint orientation	0.24[*]	0.12	––		
Social skills					
General social skills	0.17[*]	0.13	0.40[*]	––	
Procedural information	0.12[*]	-0.07	0.12[*]	0.12[*]	––

[*]p<0.05.

Jacobs, et al. The structure of medical competence and results of an OSCE.

Table 7
Correlations between the five scales of history taking skills and four external criteria (n=593, except patient-centredness/ quality (n=191)

SCALES OF HISTORY TAKING SKILLS	TUTOR'S GLOBAL APPRECIATION OF HISTORY TAKING SKILLS	KNOWLEDGE ESTIMATE BY TUTOR	OVERALL GRADE (BY TUTOR)	MEAN SCORE ON PRODUCT STATIONS OF THE OSCE
Patient-centredness/frequency	0.02	0.02	0.00	-0.12
Patient-centredness/quality	0.16	0.10	0.14	0.10
Complaint orientation	0.17[*]	0.26[*]	0.13	-0.10
General social skills	0.29[*]	0.06	0.17	0.04
Procedural information	0.06	0.05	0.03	-0.14[*]

[*]p<0.05.

DISCUSSION

The students' results in the history taking station of the OSCE at the start of the clerkships were analysed in order to gain more insight into the structure of medical competence as a subject of assessment. First, the structure of the complete checklist was examined with a factor analysis. This revealed a non-interpretable solution, because of the fact that for several items of the checklist for this OSCE station, the frequencies in the scoring category 'not shown' were quite high. Apparently, students tended to overlook the patient-centred elements (items 6-11 and 20-21). This might have been partly caused by the pressure of time, but the instruction to the students was to address only the specific history of the present complaint. Furthermore, the students were trained to pay attention to the issues of the items 6 to 11 and 20 and 21 in this part of the history taking process. And most students felt, as expressed during the assessment, that they completed this part of the history taking with the standardised patient.

The correlation between the number of performed activities and the level of performance of these activities was close to zero. This implied that the scoring categories 'not shown, poor, moderate and good' could not be perceived as a one-dimensional interval or even an ordinal scale. Therefore the checklist was analysed in parts.
The first analysis included the patient-centred intellectual items. For a better understanding, two new uncorrelated variables were introduced: the 'frequency of patient-centred intellectual items' and the 'quality of performance of patient-centred items'. Factor analysis of the remaining intellectual items showed that these could be represented by one factor labelled 'complaint orientation of history taking'. Subsequently, factor analysis of the items concerning social skills revealed two factors renamed: 'general social skills' and 'providing procedural information to the patient'.
The correlations between the scale scores of these five scales, covering an important part of the history taking

skills of the students, were low. This suggests that it is very unlikely that any one of these scales might be used to represent history taking, and even more unlikely that one such scale could represent medical competence. Apparently, the content of the history taking checklist represents very different domains, which underlines a 'multifaceted' model of medical competence. Nevertheless, the study offered no support for Metz's model[1] of four dimensions; the structure of history taking skills seems to be more complex.
In the interpretation of the results of this study the validity of the checklist of the history taking skills is an important issue. The checklist was based on a valid instrument in assessing the essential elements in history taking,[13] further scrutinised and adapted by experienced clinicians to strengthen its validity in the given test procedure. The checklist history taking is directed at the basic communication skills including the skills to collect medical information, independent of case-specific content. To ensure scoring is as uniform as possible, one of the two specially trained expert-observers observed the history taking stations.[12]

To examine the external validation we compared the results on the five scales of the checklist with the global appreciation of history taking skills by the tutors. These correlations were low. First, this low correlation might be due to a low content validity of the checklist. However, the checklist was put together with great care. Furthermore, the assessment procedures were aimed at skills that are specifically taught in our medical curriculum: social skills and intellectual skills in history taking are given special attention. Second, the quality of the observations by the tutors might be less thorough than expected. It is known that personal observations of a teacher in close and intensive contact with students introduce subjective elements (e.g. halo effects) in tutor judgements.[14,15] That was one of the very reasons for introducing objective structured clinical examinations in 1979.[16] Another explanation for the low correlation might be the difference in time; a four-week period is compared

Jacobs, et al. The structure of medical competence and results of an OSCE.

NOVEMBER 2004, VOL. 62, NO. 10
402

with a five-minute station in the OSCE. In conclusion, the observation that the results in the history taking station of the objective assessment were not in accordance with those of the tutors does not necessarily indicate shortcomings in the OSCE.

The OSCE described here was scheduled at the end of a training period and had to assess the general clinical competence of the students at that particular moment. Of course no final judgement of their competence in history taking may be inferred by this assessment because generalisations about a person's competence can not be based on one or two patient encounters.[17] Moreover, earlier studies have demonstrated that clinical performance is, apart from content specificity, very variable and unpredictable.[11] By comparing the results of this large group of students and the relation of these results with other outcomes, we sought to get an impression of the structure of the history taking skills of these students. It was not the purpose of this study to find differences between individuals.

The ideal final assessment of a student's medical competence will be an appraisal of his daily work in clinical practice. The final examination at our medical school consists of a four-week internship. In this internship the responsibilities of the undergraduate student resemble those of a resident, but the goals of this internship are different from a residency.

To summarise, the structure of history taking skills and medical competence is complex. An adequate theoretical basis could have an important impact on the development of education and assessment programmes both in undergraduate and in postgraduate continuing medical education. If the various scales as identified in our study indeed make up the competence of history taking, this should be taken into account, both in training and assessing this skill, also during the internships. Regarding medical competence, one might conclude that medical competence comprises at least these five elements. To accomplish proper assessment, the various components determining medical competence have to be clear. But, based on the presented results, it is clear that medical competence should be tested in a more detailed way. We recommend a structured assessment supported by a convenient checklist, with or without certain weights reflecting the educational goals of the specific programme. An interesting follow-up research design directed at the assessment of history taking would be to ask the tutors for five global marks on 'patient-centredness/frequency', 'patient-centredness/quality', 'complaint orientation', 'general social skills' and 'providing procedural information to the patient' for each student and compare these marks with the scales of the items on the checklist. Possibly this would support the generation of a short, comprehensive checklist and provide more insight into the relative importance of each scale of history taking.

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Jacobs, et al. The structure of medical competence and results of an OSCE.

NOVEMBER 2004, VOL. 62, NO. 10

403

A 48-YEAR-OLD WOMAN WITH ABDOMINAL PAIN AND FEVER

Computed tomography showed a large abdominal mass in the right lower abdomen (*figure 1*) and an intrauterine device (IUD) in situ (*figure 2*). Especially the latter took us by surprise because she did not tell us about it. After specifically asking her she told us the IUD had been in situ for 28 years.

The patient was transferred to the department of gynaecology for operative exploration of the abdominal mass. A large abscess of the right adnex and tuba, containing a lot of pus and debris, was found. The IUD was cultured and showed an *Actinomyces israelii* infection As expected typical sulphur granules were not seen *in vitro*. Pus drained shortly after starting antibiotics no longer showed Actinomyces growth. High suspicion on forehand will be helpful making it possible to culture Actinomycosis or see sulphur granules in patient material.[1,2]

Within the genus *Actinomyces,* the *Actinomyces israelii* is the most important human pathogen. It is a Gram-positive, anaerobic bacterium with a filamentous fungal-like appearance and forms part of normal flora in the mouth, gut and vagina. Infection is endogenous and there is no person-to-person spread. Actinomycosis follows local trauma and invasion of normal flora. Hard non-tender swellings develop slowly which eventually drain pus through sinus tracts, often not respecting anatomic barriers. Cervicofacial lesions are most common, but abdominal lesions after surgery and infection related to IUDs occur, frequently imitating more common conditions.[3] Penicillin is the drug of choice.[4] Surgery is reserved for cases of mass abscess formation as in our patient.

DIAGNOSIS

Actinomycosis with abscess formation.

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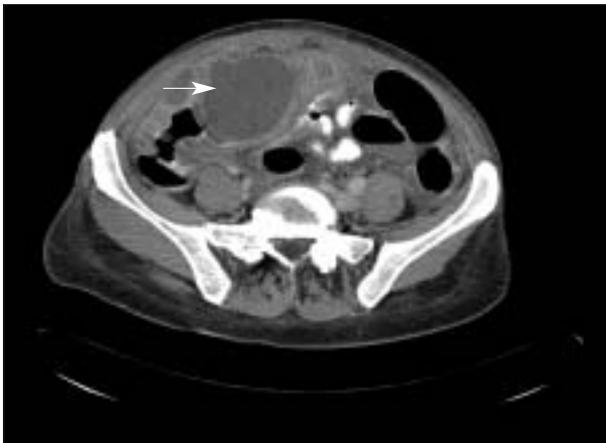
Figure 1
Computed tomography shows a large abdominal mass in the right lower abdomen (see arrow)
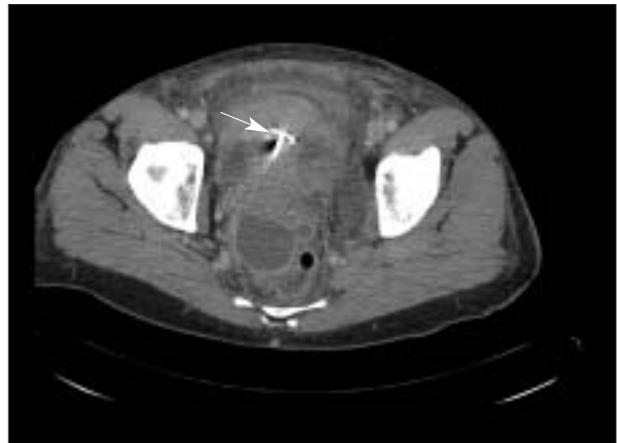
Figure 2
Computed tomography shows an intrauterine device in situ (see arrow)

'Untitled'

Judith Stolker

Judith Stolker, the artist of this month's cover, was born in Enschede in 1960. She was educated at the Academy of Arts in Enschede and Arnhem. Her work has been exhibited in several group and solo expositions, for example in Gemeentemuseum Arnhem, Apeldoorn's Museum, Galerie Gele Rijder in Arnhem, Galerie Occo in Amsterdam and also in the Dutch Biennial for Figurative Art 2004.

In her work she balances between peace and pressure. The print shown is a stencil-plate print, a simple technique that is only useful for small editions because planes are used rather than lines. These limitations make the stencil-plate technique interesting. The print is one out of a series of four prints portraying 'fruity-like' objects. These are imaginary fruits - but to those who want to see it - somewhat erotic symbols of fertility.

An original print (30 x 30 cm), seven in edition, is available at a price of € 275 each. The series of four prints can be ordered at the price of € 950 at Galerie Unita, Rijksstraatweg 109, 6573 CK Beek Ubbergen, the Netherlands, by e-mail: galerie-unita @planet.nl or see the website: www.galerie-unita.com.

Bijsluiters

Aims and scope

The Netherlands Journal of Medicine publishes papers in all relevant fields of internal medicine. In addition to reports of original clinical and experimental studies, reviews on topics of interest or importance, case reports, book reviews and letters to the Editor are welcomed.

Manuscripts

Manuscripts submitted to the Journal should report original research not previously published or being considered for publication elsewhere. Submission of a manuscript to this Journal gives the publisher the right to publish the paper if it is accepted. Manuscripts may be edited to improve clarity and expression.

Declaration

It is the author's responsibility to seek permission from the person or party concerned for the use of previously published material, such as tables and figures. In addition, persons who are recognisable on photographs must have given permission for the use of these.

Language

The language of the Journal is English. English idiom and spelling is used in accordance with the Oxford dictionary. Thus: Centre and not Center, Tumour and not Tumor, Haematology and not Hematology.

Preparation of manuscripts

Type all pages with double spacing and wide margins on one side of the paper. To facilitate the reviewing process number the pages; also we would appreciate seeing the line numbers in the margin (Word: page set-up – margins – layout – line numbers). Divide the manuscript into the following sections: Title page, Abstract, Introduction, Materials and methods, Results, Discussion, Acknowledgements, References, Tables and Figures with Legends.

A *Covering letter* should accompany the manuscript, identifying the person (with the address, telephone and telex numbers, and e-mail address) responsible for negotiations concerning the manuscript: the letter should make it clear that the final manuscript has been seen and approved by all authors. Conflicts of interest, any commercial affiliations, consultations, stock or equity interests should be specified. In the letter 1-3 sentences should be dedicated to what this study adds. All authors should sign the letter.

The *Title page* should include authors' names, degrees, academic addresses, address for correspondence including telephone, fax and e-mail, and grant support. Also the contribution of each author should be specified. The title should be informative and not exceed 90 characters, including spaces. Avoid use of extraneous words such as 'study', 'investigation' as well as priority claims (new, novel, first). Give a running title of less than 50 characters. If data from the manuscript have been presented at a meeting, list the name, date and location of the meeting and reference and previously published abstracts in the bibliography. Give a word count (including references, excluding tables and legends) at the bottom of this page.

Subheadings should not exceed 55 characters, including spaces.

Abbreviations: Measurements should be abbreviated according to SI units. All other abbreviations or acronyms should be defined on the first appearance in the text. Use a capital letter for proprietary names of substances and materials. At first mention of a chemical substance, use the correct chemical designation as well as the generic name.

The *Abstract*, not exceeding 200 words, should be written in a structured manner and with particular care, since this will be the only part of the article studied by some readers. In original articles, the abstract should consist of four paragraphs, labelled Background, Methods, Results, and Conclusion. They should briefly describe the problem being addressed in the study, how the study was performed and which measurements were carried out, the most relevant results, and what the authors conclude from the results.

The *Introduction* should be brief and set out the purposes for which the study has been performed.

The *Materials and methods* should be sufficiently detailed so that readers and reviewers can understand precisely what has been done without studying the references directly. The description may be abbreviated when well-accepted techniques are used.

The *Results* should be presented precisely without discussion.

The *Discussion* should directly relate to the study being reported. Do not include a general review of the topic, but discuss the pertinent literature.

Acknowledgement: All finding sources should be credited here. Also a statement of conflicts of interest should be put here.

References should be numbered consecutively (in square brackets) as they appear in the text. Type the reference list with double spacing on a separate sheet. References should accord with the system used in Uniform requirements for manuscripts submitted to biomedical journals (N Engl J Med 1991;324:424-8).
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.

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Please note that the first six authors should be listed; when seven or more, list only the first three and add *et al.* Do not include references to personal communications, unpublished data or manuscripts either 'in preparation' or 'submitted for publication'. If essential, such material may be incorporated into the appropriate place in the text. Recheck references in the text against reference list after your manuscript has been revised.

Tables should be typed with double spacing each on a separate sheet, numbered consecutively with Arabic numerals, and should contain only horizontal lines. Provide a short descriptive heading above each table with footnotes and/or explanation underneath.

Figures must be suitable for high-quality reproduction. Submit line drawings made in Word or other computer programmes but not in a PowerPoint file. India ink drawings or sharp, strongly contrasting photographic prints on glossy paper are also acceptable. Lettering should be complete, of professional quality, and of a size appropriate to that of the illustration of drawing, with the necessary reduction in size taken into account. Figures should be no larger than 12.5 x 18 cm. Submit half-tone illustrations as black-and-white prints on glossy paper, with as much contrast as possible. Identify each figure on the back with a typed label, which shows the number of the figure, the name of the leading author, the title of the manuscript and the topside of the figure. Colour figures are occasionally possible and will be charged to the authors.
Legends for figures should be typed, with double spacing, on a separate sheet.

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Brief reports containing concise reports on original work will be considered for publication. Case reports which are relevant for understanding the pathophysiology or clinical presentation of disease may also be accepted under this heading. Articles published in this section should be no longer than 1000 words, and be supplied with a summary of about 60 words, preferably no more than two figures and/or tables, and no more than 15 references.

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Manuscripts should be sent to the Editor in chief, Prof. J.W.M. van der Meer, University Medical Centre St Radboud, Department of General Internal Medicine, PO Box 9101, 6500 HB Nijmegen, the Netherlands, tel.: +31 (0)24-361 04 59, e-mail: g.derksen@aig.umcn.nl. They should be submitted in four complete copies, which include four sets of the figures; authors should retain one copy of the manuscript. Rejected manuscripts will not be returned to the author unless specially requested at the time of submission.

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After external and editorial review of the manuscript, the authors will be informed about acceptance, rejections or revision. Unless stated otherwise in our letter, we require revision within three months.

Acceptance

After acceptance we prefer electronic submission of text and figures, either by e-mail to g.derksen@aig.azn.nl or on floppy disk. A disk plus two final and exactly matching printed versions should be submitted together. It is important that the file saved is in the native format of 'Word' or any other computer programme used. Label the disk with the name of computer programme used, your name, and the name of the file on the disk.

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