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EDITORIAL

Side effects of anticytokine strategies

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ABSTRACT

Anticytokine strategies probably represent the most important breakthrough in the treatment of inflammatory diseases in the last decade. However, blocking the bioactivity of proinflammatory cytokines, crucial activators of host defence, has proved to be accompanied by an increased susceptibility to infections, especially with *Mycobacteria*, *Salmonellae* and fungal pathogens. Multiple mechanisms for these side effects have been proposed, such as inhibition of gamma-interferon production, decreased expression of pattern-recognition receptors, and leucocyte apoptosis. Caution is therefore warranted when these treatments are given to patients with an increased risk for infections. A range of side effects other than infection have been reported.

Treatment strategies interfering with proinflammatory cytokines such as tumour necrosis factor (TNF) α and interleukin-1 (IL-1) constitute a breakthrough in the treatment of rheumatoid arthritis (RA) and other inflammatory disorders. However, some 10 to 15 years ago it was demonstrated in experimental animals that treatment with antibodies against TNF was deleterious in mycobacterial infections, fungal infections and abscesses. The exact mechanisms by which interference with TNF produced these results were not entirely clear, but it was concluded that containment of micro-organisms within granulomas and abscesses was not achieved or maintained.[1-3]

Based on these observations, it was easy to predict that large-scale and prolonged anti-TNF treatment in humans would lead to infections, especially by organisms that induce a granulomatous response. Indeed, such complications (especially mycobacterial and *Salmonella* infections) were readily encountered, but still seemed to come as a surprise to the medical community.

In this issue of the journal, Efde and colleagues report a case of tonsillar tuberculosis, a rare manifestation of this infectious disease, occurring during anti-TNF treatment.[4] The occurrence of these infections has important implications for pretreatment assessment of patients, and guidelines for this purpose are appearing, also in the Netherlands.[5] Two years ago, the Netherlands Journal of Medicine published a state-of-the-art review by Arend *et al.* on this topic with a detailed account of the literature and a proposal for the management of patients at risk.[6] The patient reported in this issue of the journal received a six-month course of isoniazid for latent tuberculosis. As noted in the review[6] and by the authors of the case report,[4] a period of six months of isoniazid is not optimal. It also implies that the risk of reactivation of tuberculosis during anti-TNF treatment in patients harbouring dormant bacilli should not be underestimated.

It is interesting that the risk for infection is greater with the monoclonal antibodies against TNF (infliximab and adalimumab) than with the TNF receptor construct etanercept: during infliximab therapy the risk is estimated to be 200 per 100,000 treatments, with etanercept it is 9 per 100,000.[7] Theoretically, one would expect differences between the various types of anti-TNF drugs, as they differ in their capacity to interact with TNF-α and TNF-β (lymphotoxin), and with membrane-bound TNF. Another

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interesting, not well-explained observation is that treatment with the recombinant interleukin-1 receptor antagonist, IL-1Ra (anakinra), does not seem to lead to excess infection.

How inhibition of TNF impairs host defence in patients is still enigmatic, but several mechanisms have been suggested. Firstly, blockade of TNF itself can impair host defence, as TNF is known to activate the microbicidal properties of neutrophils and macrophages.[8] Secondly, TNF blockade can inhibit secondary activation of the cytokine cascade. We have demonstrated in patients with a serious *Salmonella* infection that interferon-γ production was strongly inhibited.[9] The role of the latter cytokine in host defence against micro-organisms is much better understood: a deficient response to this cytokine has been shown to lead to serious infections.[10-12] Important questions that remain are whether all patients who receive anti-TNF treatment respond with a down-regulation of the interferon-γ response, and whether we can predict the risk for infection by assessing the production of this cytokine. It is also tempting to speculate that the capacity to down-regulate the interferon-γ response explains the difference in occurrence of infection between IL-1 inhibition and TNF inhibition, but more research is needed to answer this question. Other mechanisms of anti-TNF treatment include down-modulation of pattern recognition receptors such as TLR4,[9] and leucocyte apoptosis.[13] One may also ask the question whether anticytokine treatment, for example in patients with rheumatoid arthritis, has more effects that are not intended. A range of side effects other than infection have been reported, albeit with a lower incidence.[14]

Treatment with TNF inhibitory agents has been associated with rare cases of onset or exacerbation of demyelinating disorders, which met with a partial or complete response when treatment was stopped. In addition, despite the elevated TNF concentrations in the cerebrospinal fluid and in the circulation of multiple sclerosis (MS) patients, blocking this cytokine resulted in a worsening of the disease.[15] The mechanisms underlying this side effect are still unknown.

Development of autoantibodies including antinuclear antibody (ANA) and anti-double-stranded DNA have been reported during therapy with anti-TNF agents. The clinical relevance of this is uncertain, although post-marketing surveillance reports mention cases of autoimmune diseases, especially leucocytoclastic vasculitis and lupus-like syndrome, improving after therapy was discontinued.

Concerns have been raised about haematological disorders, especially non-Hodgkin's lymphoma, and cytopenia during anti-TNF therapy. Very few cases have been reported in patients with long-lasting RA receiving multiple drugs. The role of anti-TNF drugs is therefore unknown.

Congestive heart failure proved to worsen by TNF blockade, despite earlier studies predicting the opposite: chronic heart failure (CHF) was associated with elevated production of TNF. Trials intended to show the benefit of suppressing TNF in CHF patients met with increased mortality in the anti-TNF group compared with placebo.[16] However, one should be prudent when interpreting the onset of CHF in patients with RA receiving anti-TNF therapy, as cardiovascular diseases are a leading cause of death among these patients.

Perhaps more interestingly, therapy of RA patients with TNF blockers might also have beneficial consequences, other than those related to the inflamed joints.

An increased mortality due to cardiovascular and cerebrovascular diseases is seen in RA patients when compared with the general population. The contribution of inflammation to the development of atherosclerosis and insulin resistance is now regarded to be more and more important, and TNF has emerged as playing a key role in these processes. In addition, markers of inflammation, such as C-reactive protein (CRP), are now considered to be important predictors of future acute cardiovascular events. In that respect, we recently investigated whether the profile of cardiovascular risk factors in such patients ameliorates during anti-TNF treatment.[17] This would not be unexpected, since TNF is known to increase interleukin-6 (IL-6) and CRP and induce proatherogenic changes in lipid profile.

We found that anti-TNF treatment with adalimumab enhanced the concentrations of HDL cholesterol and decreased the concentrations of CRP and IL-6 within 14 days. To what extent these changes remain during prolonged observation and translate into a lower cardiovascular risk is the subject of future studies.

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REVIEW

Local and systemic thrombolytic therapy for acute deep venous thrombosis

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ABSTRACT

This article presents a review of the treatment of lower-extremity deep venous thrombosis (DVT) with systemic and catheter-directed thrombolysis (CDT) and percutaneous mechanical thrombectomy (PMT). Standard treatment including anticoagulation therapy and compression stockings may not be entirely adequate, because a significant proportion of patients eventually develop post-thrombotic syndrome (PTS). Thrombolytic agents might offer a potential advantage because they cause faster and more complete clot resolution, which may reduce or prevent residual vein stenosis and valve damage.

Thrombolytic therapy results in greater lysis, but also in higher complication rates than does anticoagulation alone. Major bleeding occurs in 11% of patients treated with thrombolytic therapy. The incidence of PTS tends to be lower in patients treated with thrombolytics. However, several methodological flaws limit the conclusions with respect to reduction in PTS.

No adequate randomised controlled trials have been performed comparing CDT or PMT with conventional therapy. Given the current data, thrombolytic treatment, CDT or PMT should not be applied except in extraordinary cases. First, the long-term effectiveness in terms of reducing PTS, although possible, remains uncertain. Second, the risks of thrombolytic therapy and PMT are higher. Third, current conventional therapy is relatively inexpensive, convenient and safe.

INTRODUCTION

Deep venous thrombosis (DVT) is an important disease with serious clinical sequelae. Its annual incidence is one per 1000 patients, but the incidence increases with age.[1-3] The therapeutic goals for treating the patient with acute DVT include prevention of pulmonary embolism (PE), prevention of recurrent thrombosis and preservation of venous valve function. Success in the achievement of these clinical goals will minimise the morbidity and mortality of PE and will diminish the long-term sequelae of the post-thrombotic syndrome (PTS).

The current standard of care includes systemic anticoagulation with unfractionated heparin (UH) or low-molecular-weight heparin (LMWH) followed by oral anticoagulants.[4,5] Such a regimen, however, does not promote lysis to reduce the thrombus load, nor does it contribute to restoration of venous valve function. Anticoagulation alone, therefore, might not sufficiently protect the limb from PTS. Catheter-directed thrombolysis (CDT) and percutaneous mechanical thrombectomy (PMT) have been proposed as a new treatment for patients with DVT. Application of these techniques could potentially result in a lowering of the PTS syndrome by preservation of the venous valve function. This article provides a comprehensive review of the literature evaluating the efficacy and safety of systemic thrombolysis and CDT and PMT in patients with DVT, with the focus on PTS.

CLINICAL CONSEQUENCES OF DVT

In the acute phase, venous obstruction leads to impaired venous return and therefore most patients experience leg

[**]Th. Thien was not involved in the handling and review process of this paper.

pain and swelling. Patients with extensive thrombosis may experience more severe symptoms and on rare occasions develop limb-threatening ischaemia. PE, with its attendant mortality, is the most devastating complication of acute DVT.[6] Chronically, DVT results in a variable degree of venous obstruction and valvular incompetence. These changes can lead to PTS.[7]

Pathophysiology of PTS

PTS refers to a spectrum of post-thrombotic chronic venous diseases attributable to venous hypertension and stasis affecting a limb in which a DVT has previously occurred. The spectrum of PTS can encompass several combinations of symptoms in various degrees of severity. These include a chronic feeling of leg heaviness, leg aching and venous claudication, oedema, venous varicosities, and chronic trophic skin changes ranging from hyperpigmentation to frank nonhealing ulceration to fibrotic scarring.[8-10]

The pathophysiology is thought to be multifactorial, including venous obstruction and valvular incompetence; inflammatory damage caused by the thrombotic process and subsequent scarring is a likely mechanism. Valvular incompetence develops most frequently in segments affected by thrombosis and seldom develops in segments initially free of thrombus, with total thrombotic occlusions resulting in the highest risk for subsequent valve insufficiency.[11-14] Unlike valvular incompetence, which can develop shortly after acute DVT, the onset of dermatological manifestations of PTS tends to be much more delayed, with symptoms usually occurring within two years after the initial DVT episode.[9,15,16]

CONVENTIONAL ANTICOAGULANT THERAPY

Current conventional treatment of DVT consists of anticoagulation and the use of compression stockings. Anticoagulation therapy consists of subcutaneous LMWH or intravenous UH initially, followed by oral anticoagulants. LMWH is continued for at least five days and coumarin therapy for at least three months, the total duration varying according to underlying risk factors for recurrence. In general, this approach to treatment is effective and safe in most patients.[4,17-20] Anticoagulation therapy has no direct thrombolytic effect, and thrombus recanalisation largely depends on the effectiveness of the endogenous fibrinolytic system and the initial thrombus load. The risk of major complications in large randomised trials of LMWH is low: fewer than 5% have recurrent venous thromboembolic events, fewer than 2% have clinically significant bleeding, and fewer than 2% have symptomatic PE.[4,18,21,22]

No major randomised trials of treatment in the initial phase have included PTS as a primary endpoint. Adjunctive treatments such as compression stockings have been shown to reduce the incidence of the PTS by 50%.[23] However, a risk of moderate to severe PTS of about 10% is reported in patients who receive appropriate anticoagulation and compression therapy. Proponents of thrombolytic therapy argue that this rate is high enough to warrant interventional treatment strategies.[24,25]

METHODS

Nonconventional thromboablative types of therapy in acute DVT include systemic thrombolytic therapy, catheter-directed regional thrombolytic therapy (CDT) and percutaneous mechanical thrombectomy (PMT).

A study using the electronic literature (PubMed) was performed using the keywords deep venous thrombosis, thrombolysis, catheter-directed thrombolysis and mechanical thrombectomy. Literature was reviewed up to January 2004. Eighteen controlled trials were identified comparing systemic thrombolytic therapy with standard treatment.[26-42] Twelve studies compared streptokinase with heparin (468 patients), two trials compared urokinase with heparin (117 patients) and four trials compared tissue plasminogen activator with heparin (150 patients). There were eight trials reporting the incidence of PTS after thrombolysis. Only one trial compared catheter-related thrombolysis with standard anticoagulant treatment.[43] There are no trials comparing PMT and conventional therapy. For this reason also non-randomised trials evaluating CDT and PMT are discussed.

SYSTEMIC THROMBOLYTIC THERAPY

The rationale for an aggressive thromboablative approach in acute DVT might be twofold. In the short term, it consists of preventing PE, achieving rapid reduction of pain and swelling of the involved leg, and, when applicable, preventing or allowing more effective management of phlegmasia cerulea dolens and venous gangrene. The long-term endpoint of treatment of an acute DVT episode relates mainly to the prevention of PTS. Rapid thrombus resolution may offer a potential for prevention of PTS based on the known favourable effect on the preservation of venous valvular function. It might also prevent the development of obstructive disease because it prevents organisation of an occlusive thrombus, which leads to downstream venous hypertension.

Tables 1[26-42] and *2*[29,38,39,44-48] show a summary of the randomised controlled trials that have compared lytic therapy with standard heparin in the acute phase and in the long-term. It has to be noted that there are no trials comparing thrombolytic therapy with LMWH.

Table 1
Randomised trials comparing systemic thrombolytic and heparin therapy for deep venous thrombosis

AUTHOR (YEAR)	NUMBER			VENOGRAPHIC RESULTS (RESOLUTION)			MORTALITY	PE	MAJOR BLEEDING
	TOTAL	EVALUBLE	TREATMENT	COMPLETE N (%)	PARTIAL N (%)	NONE N (%)	N (%)	N (%)	N (%)
Browse	10	5	Heparin	0	0	5 (100)	0	0	0
(1968)		5	SK	3 (60)	1 (20)	1 (20)	0	0	0
Robertson	16	8	Heparin	0	3 (37)	5 (63)	1 (10)	ND	1 (13)
(1968)		8	SK	0	7 (87)	1 (13)	0	ND	3 (38)
Kakkar	20	9	Heparin	2 (22)	2 (22)	5 (56)	2 (20)	1 (10)	2 (20)
(1969)		9	SK	6 (67)	1 (11)	2 (22)	0	0	2 (20)
Robertson	16	7	Heparin	2 (29)		5 (71)	0	0	1 (14)
(1970)		9	SK	6 (67)		3 (33)	1 (11)	4 (44)	ND
Tsapogas	34	15	Heparin	1 (7)		14 (93)	0	1 (7)	ND
(1973)		19	SK	10 (53)		9 (47)	0	0	ND
Duckert*	134	42	Heparin	0	4 (10)	38 (90)	0	5	58 (62)
(1975)		92	SK	39 (42)	23 (25)	30 (33)	0	7	2 (5)
Porter	50	26	Heparin	1 (4)	20 (77)	5 (19)	0	0	1 (4)
(1975)		23	SK	6 (26)	15 (65)	2 (9)	1 (4)	0	4 (17)
Marder	24	12	Heparin	0	3 (25)	9 (75)	0	ND	ND
(1977)		12	SK	5 (42)	2(16)	5 (42)	1	ND	ND
Arnesen	42	21	Heparin	5 (24)		16 (76)	0	0	3 (14)
(1978)		21	SK	15 (71)		6 (29)	0	1 (5)	3 (14)
Eliott	51	25	Heparin	0	ND	ND	2 (8)	2 (8)	0
(1979)		23	SK	9 (39)	12 (52)	2 (9)	0	1 (4)	2 (8)
Watz	35	17	Heparin	1 (6)	5 (29)	11 (65)	0	1	0
(1979)		18	SK	8 (44)	4 (22)	6 (34)	0	1	0
Schulman	38	19	Heparin	2 (11)	ND	ND	0	0	1 (5)
(1986)		17	SK	7 (41)	ND	ND	0	0	3 (18)
Jeffrey	40	20	Heparin	1 (5	0	19 (95)	ND	ND	ND
(1986)		20	SK	11 (55)	0	9 (45)	ND	ND	ND
Turpie I	24	12	Heparin	2 (17)		10 (83)	0	ND	1 (8)
(1990)		12	rt-PA	9 (75)		3 (25)	0	ND	4 (33)
Turpie II	59	30	Heparin	7 (23)		23 (77)	0	ND	1 (3)
(1990)		28	rt-PA + heparin	13 (46)		15 (54)	0	ND	1 (3)
Goldhaber	65	11	Heparin	0	2 (18)	9 (82)	0	ND	0
(1990)		32	rt-PA	2 (6)	18 (56)	12 (38)	0	ND	1 (3)
		17	rt-PA + heparin	1 (6)	8 (47)	8 (47)	0	ND	0
Goldhaber	361	9	Heparin	1	5	3	0	ND	1
(1996)		8	rUK	1	5	2	0	ND	0
Schweizer	150	50	Heparin	1 (2)	9 (18)	40 (80)	0	0	0
(2000)		50	UK + heparin	17 (34)	23 (36)	10 (20)	0	4 (8)	4 (8)
		50	SK + heparin	20 (40)	20 (40)	10 (20)	0	5 (10)	5 (10)

*PE = pulmonary embolism; SK = streptokinase; UK = urokinase; rUK = recombinant urokinase; rt-PA = recombinant tissue plasminogen activator; ND = not determined; *not randomised.*

Short-term efficacy

The results of randomised controlled trials assessing the short-term efficacy of streptokinase, urokinase and rt-PA compared with heparin are summarised in *table 1*.[26-30,32,33,35-41,48] Most of these trials demonstrate that systemic thrombolytic therapy more often leads to complete or partial resolution than does heparin therapy. Complete lysis occurred in 26 to 67% and 0 to 22% of patients, respectively. Although at least some degree of lysis has been reported in 50 to 70% of patients treated with thrombolysis, no single study has had sufficient power to prove its efficacy in comparison with standard anticoagulation. Previous studies suggest that newer and nonocclusive thrombi are more likely to undergo successful lysis when compared with older and occlusive thrombi.[49]

Long-term efficacy

Eight studies (173 patients) were identified comparing lytic therapy with UH in which long-term efficacy was assessed.[29,38,39,44-48,50] An additional study has been published in which patients were randomised to one of several thrombolytic regimens or UH (250 patients).[39] Duration

Table 2
Long-term results of systemic thrombolytic therapy

AUTHOR (YEAR)	NUMBER OF PATIENTS		DURATION OF FOLLOW-UP	TREATMENT	RESULTS		
					VENOGRAMS		
	INITIAL	LONG-TERM			NORMAL N (%)	FUNCTIONAL PTS* N (%)	CLINICAL PTS N (%)
Kakkar (1969)	20	8	6-12 months	Heparin	1 (13)	7 (87)	ND
		7		SK	4 (57)	3 (43)	ND
Bieger (1976)	10	5	3-4 months	Heparin	1 (20)	4 (80)	2 (40)
		5		SK	4 (80)	1 (20)	0
Common (1976)	50	12	4-18 months	Heparin	1 (8)	11 (92)	6 (50)
		15		SK	6 (40)	9 (60)	5 (33)
Johansson (1979)	57	3	9-12 years	Heparin	2 (66)	1 (33)	2 (66)
		5		SK	0	3 (100)	4 (80)
Elliott (1979)	51	20	19 months	Heparin	ND	ND	18 (90)
		23		SK	10 (50)	10 (50)	8 (35)
Arnesen (1982)	42	18	6.5 years	Heparin	0	18 (100)	12 (67)
		17		SK	7 (44)	9 (56)	4 (24)
Schulman (1986)	38	18	2-108 months	Heparin	4 (36)	7 (64)	11 (61)
		17		SK	1 (14)	6 (86)	11 (65)
Schweizer (2000)	250	46	12 months	Heparin	5 (11)	41 (89)	41 (89)
	46			SK (syst) + heparin	23 (50)	23 (50)	23 (50)
	46			UK (syst) + heparin	14 (30)	32 (70)	32 (70)
	50			UK (locoregional) + heparin	13 (26)	37 (74)	37 (74)
	50			Rt-PA + heparin	11 (22)	39 (78)	39 (78)

*PTS = post-thrombotic syndrome; SK = streptokinase; UK = urokinase; rt-PA = recombinant tissue plasminogen activator, *measured using venography or duplex.*

of follow-up varied from two months to six years. Most of the studies invariably did not use a validated scoring system for assessment of PTS, but relied on clinical assessment. These assessments were performed at different intervals in each study and were not always blinded to the treatment allocation, and in some of the trials assessments were limited because of significant numbers of patients lost to follow-up.

Aggregating the data from these studies, the long-term risk of developing PTS in the thrombolytic groups is 0 to 80%, whereas in the unfractionated heparin group it is 40 to 90%.

The largest study demonstrated relatively poor functional results (low reflux pathology) in heparin control patients, giving rise to more symptoms of PTS.[39] They also observed that patients affected by thromboses in the pelvic region seemed to benefit less from lytic treatment, which is known due to early collateral formation. Lysis medication may, thereby, fail to reach thromboses in pelvic veins due to circulatory bypasses.

Complication rates

Potential complications of thrombolytic therapy include bleeding and PE. In a meta-analysis Lensing and Hirsh reported major bleeding events in 13.2% of patients treated with systemic streptokinase or recombinant tissue plasminogen activator (rt-PA) compared with 3.5% of patients treated with heparin. Systemic treatment with rt-PA resulted in one major haemorrhage for every 15 patients treated.[51] Aggregating the data across studies in *table 1* shows that 9% (range 0 to 38%) of patients receiving thrombolytic agents have a major bleed compared with only 5% (range 0 to 22%) of patients receiving UH. The wide range can be explained by more aggressive diagnostic and follow-up protocols in earlier studies and by the variable definitions of 'major haemorrhage'. There was no significant difference in bleeding risk according to route of administration or dose. Haemorrhage following thrombolytic therapy most commonly occurs at vascular puncture sites, although spontaneous haemorrhage, especially gastrointestinal, retroperitoneal and intracranial, may also occur. Older age, a higher body mass index, and the performance of pulmonary angiography have been identified as significant predictors of bleeding.

Before initiating thrombolytic therapy, patients should undergo a thorough evaluation to elicit factors that increase the risk of major haemorrhage. A striking study is that of Markel *et al.*[52] in which only 15 (7%) of 209 patients with DVT exhibited no contraindications for thrombolytic treatment.

Risk of PE while receiving the thrombolytic agent is a theoretical concern. Lensing and Hirsh demonstrated that in contrast to the haemorrhagic risk, the incidence of clinically significant PE was quite low.[51] However,

Schweitzer's data suggest that there is an increased risk as 4.5% of patients suffered a PE while on lytic therapy.[39] Furthermore the prolonged infusion times (two to three days) typically required to treat iliofemoral DVT can be difficult to tolerate for some patients, and complications may become more frequent with longer infusion durations. Also the cost of thrombolytic infusion, multiple venograms, repeat laboratory studies and the intensive care unit monitoring required for thrombolytic therapy in many centres is substantial.

Failure of lytic therapy

Reasons for lytic therapy to fail include extensive DVT in which the plasminogen activator does not contact the clot; old, organised thrombus; inadequate fibrinolytic response; and premature termination of lytic infusion.[49] The success of lysis is related to the amount of fibrin bound to plasminogen within the thrombus and, therefore, correlates with the age of the thrombus. Treatment of patients whose thrombus is more than one week old is less likely to be successful. Unfortunately, clinicians cannot accurately determine the age of the clot but must rely on patient's symptoms, which in many cases are not closely related.

In most centres only patients with extensive venous thrombosis are treated with thrombolytic therapy. Because these patients frequently have iliofemoral venous thrombosis, they are likely to have the poorest long-term outcome. This patient selection process represents an inherent bias in evaluation of outcome based on therapy. In such patients, the venous system is frequently occluded by the thrombus and there is no blood flowing through the veins involved.

CATHETER-DIRECTED THROMBOLYSIS

Local-regional thrombolytic therapy has emerged in the past decade as a possible superior approach, allowing delivery of the pharmacological thrombolytic agent directly into the venous thrombus. This technique has evolved to address the main limitations of systemic thrombolysis; namely, unpredictability of thromboablative effect, high risk for haemorrhagic complications and high rate of patient exclusion from therapy because of the need to adopt stringent selection criteria to avoid haemorrhagic complications.

The most common agents used are urokinase and rt-PA. Two groups of techniques have been developed.[53] The first is catheter-directed thrombolysis, which relies on administration of the thrombolytic agent directly into the clot with use of a variety of infusion catheters or wires and from various approaches. The second is flow-directed regional thrombolytic therapy, which is based on the direct regional infusion of concentrated thrombolytic agent from an ipsilateral dorsal foot vein into the deep venous system. Although the latter approach has the advantage of allowing regional thrombolysis of the crural veins, which are typically difficult to access with use of catheter-directed techniques, it is more time-consuming and requires larger doses of thrombolytic than catheter-directed protocols.[53,54] Postprocedurally, all patients should be started on a long-term anticoagulation regimen with a target INR of 2.5 to 3.0 for three months unless contra-indications exist.

Only one randomised controlled study comparing CDT *vs* conventional therapy has been performed.[43] This trial is not reliable, since only 35 of 207 patients were included in the study. For this reason also the nonrandomised trials are being discussed (*table 3*).[55-69]

Several small series have demonstrated a high efficacy rate, with reported complete or substantial recanalisation rates of 60 to 83%.[61-63,66,68,69] The success rate of CDT appeared to be increased by adjunctive procedures such as angioplasty, stent placement and mechanical thrombectomy. So far, the largest published experience with this approach in lower-extremity DVT has been from the Venous Thrombolysis Registry, which reported a collective multicentre experience with 287 patients (303 limbs) in whom one-year follow-up was available.[60,70] The location of DVT was in the iliofemoral segment in 71% of patients with involvement of the inferior vena cava (ICV) in 21%. Complete thrombolysis was achieved in 31% of cases, whereas partial (>50%) thrombolysis with restoration of forward flow was achieved in 52% of patients. Complications included an 11% incidence of major bleeding that required transfusion of blood products and a 16% incidence of minor bleeding. The risks of intracranial haemorrhage and death were 0.2 and 0.4% respectively. Although the overall rate of valvular reflux on follow-up was 58%, valvular reflux occurred in only 28% of patients in whom complete thrombolysis was achieved. Comerota *et al.* demonstrated that patients treated with CDT had better functioning and well-being, compared with patients treated with anticoagulation alone.[71] Despite the possible promise of the data, the Venous Registry was not a randomised trial and lacked a control group treated with standard anticoagulation. Therefore the data cannot be used to establish a new standard of care for the treatment of acute DVT.

The most common complication during CDT is bleeding, either local from the access site or remote from onset of a systemic thrombolytic state. Reported rates of major bleeding requiring transfusion vary widely (0 to 25%), depending on the dosing regimen, duration of infusion, extent of concomitant anticoagulation and the specific

Table 3
Catheter-directed thrombolysis for DVT

AUTHOR (YEAR)	N	THERAPY	MEAN TIME OF LYSIS (HR)	SIGN RESO-LUTION N (%)	PARTIAL RESO-LUTION N (%)	NO RESO-LUTION N (%)	PTA N	STENT N	MAJOR BLEED-ING N	PE N	DEATH N
Molina (1992)	12	UK	70	11 (92)	1 (8)	0	10	5	0	0	0
Palombo (1993)	6	rt-PA / heparin*	*	6 (100)	0	0	0	0	0	0	0
Emanuelli (1995)	25	UK/SK	48	17 (68)	8 (32)	0	0	0	0	0	0
Semba (1996)	32	UK	30	27 (84)	3 (9)	2 (6)	22	20	0	0	0
Verhaeghe (1997)	24	rt-PA	30	19 (79)	5 (21)	0	0	9	6	0	0
Raju (1997)	24	UK	41	17 (71)	4 (17)	3 (12)	12	6	0	0	
Bjarnason (1997)	77	UK	75	61 (79)	0	16 (21)	46	34	5	1	0
Mewissen (1999)	312	UK	53.4	258 (83)	54 (17)	0	ND	105	54	6	2
Comerota (2000)	54			45 (83)	0	9 (17)			6	0	0
Horne (2000)	10	rt-PA	24-72	9 (90)	1 (10)	0	0	0	1	2	0
Aburhama (2001)	18	UK		15 (83)	1 (5)	2 (11)		10	2	0	0
Chang (2001)	10	rt-PA		9 (90)	1 (10)	0	0	0	0	0	0
Elshawary (2002)**	17 18	Heparin SK		0 11 (61)	0 7 (39)	17 (100) 0	0 1	0 1	0 0	1 0	0
Castaneda (2002)	25	Reteplase		23 (92)	0	2 (8)		13	1	0	0
Burkart (2002)	5	Tenecteplase		4 (80)	0	1 (20)		0	0	0	0
Cho (2003)***	5	UK		5 (100)	0	0		2	0	0	0
Grunwald (2004)	38 32 12	UK tPA rPA	40.6 30.8 24.3	27 (71) 21 (66) 6 (50)	10 (26) 10 (31) 6 (50)	1 (3) 1 (3) 0	0 0 0	0 0 0	2 1 1	ND ND ND	0 0 0

*UK = urokinase; rt-PA = recombinant tissue plasminogen activator; SK = streptokinase; ND = not determined; *rt-PA alternating with heparin infusion; **randomised study (only 35 of 207 patients were included); ***patients with protein C and S deficiency.*

thrombolytic agent used. It has been shown that prolonged infusions are associated with increased frequency of haemorrhagic complications, with intracranial bleeding occurring in as many as 3% of patients receiving systemic treatment.[72,73] Other complications include PE, infections and sepsis. The need for ICV filtration during endovascular management of extensive DVT has been debated. Furthermore, although the medical literature indicates that CDT of proximal venous thrombosis is quite successful on a short-term basis, it does not address the long-term issue PTS prevention.

PERCUTANEOUS MECHANICAL THROMBECTOMY

Since outcomes might be optimised with maximum clot removal, and because thrombolytic agents are less effective on subacute or chronic thrombus, PMT has emerged as a potentiator of pharmacological therapy. In addition, some patients with absolute contraindications to pharmacological thrombolysis may be candidates for mechanical lysis. Many devices have been developed recently, most using one of the following mechanisms to remove clot: rheolytic aspiration, mechanical aspiration or ultrasonic lysis. Some devices are designed to use both mechanical fragmentation and pharmacological lysis.[74,75]
The use of PMT might offer advantages in DVT. Flow can be established more rapidly, even though achieving complete or near-complete thrombus ablation often requires a combination of pharmacological and mechanical techniques. Furthermore it can be used primarily in situations in which rapid venous decompression and restoration of flow is crucial.[76]

Technique

The extent of thrombus is determined by imaging with ultrasound and computed tomography. Cross-sectional images also reveal other pertinent anatomical factors such as May-Thurner syndrome, osteophytes, tumours or masses. Access is obtained peripheral to the thrombosed segment and an anterograde approach is used. A single wall puncture of the ipsilateral popliteal vein is made under ultrasound guidance. If the popliteal vein is thrombosed, the proximal posterior tibial vein may be cannulated. Venograms are performed to delineate the extent of thrombus. Combined mechanical thrombectomy and pharmacological lysis can take place.

There are no controlled studies comparing PMT and conventional anticoagulant treatment. Recent trials evaluating PMT are described in *table 4*.[77-80] It has to be noted that these studies evaluated only a small selection of patients. Potentially significant complications with PMT are PE and valve damage.[74,78,81,82] Because the goal of treatment is to improve quality of life by increasing the extent of lysis while minimising complications and cost, prospective randomised studies comparing PMT *vs* conventional treatment should be performed. Patients should be followed for at least two years to detect valve insufficiency and signs and symptoms of PTS.

CONCLUSION

It is difficult to draw definitive conclusions based on the published data on thrombolysis, since studies have included relatively small numbers of patients, a range of thrombolytic regimens, and varying durations of follow-up. Furthermore, outcomes, including the degree of clot lysis and the incidence of the PTS, have been assessed using a range of modalities.

When compared with anticoagulation, thrombolytic therapy for DVT leads to superior short-term venous patency and a higher risk of major haemorrhage but no difference in the rates of PE and mortality.

It is not clear how many patients with DVT are actually candidates for thrombolytic therapy.

One study, for example, found that 194 out of 209 patients (93%) had a contraindication for thrombolysis, most often recent surgery.[52] Elshawary *et al.* also included only 35 out of 207 patients.[43]

Based on this review, there is no advantage in using any thrombolytic agent over another, or using local *vs* systemic administration. There is a need to further evaluate CDT and PMT. CDT instils the thrombolytic agent directly into the thrombus and can be combined with mechanical removal of thrombus using a suction catheter or stenting of a residual clot. This type of therapy has been suggested as an alternative to standard therapy based on a better lysis rate of 60 to 80%. Unfortunately, because these rates are derived from case series and patient registry data, they are susceptible to selection or reporting bias and the true benefit may be lower. Furthermore, the bleeding rate with this therapy is considerably higher than rates with conventional therapy, even with this select population. It should be noted that, although CDT and PMT techniques offer advantages of allowing faster and more complete clot clearance, which translate into remarkably faster symptom resolution, to date there have been no randomised trials comparing this form of therapy with conventional anticoagulation in terms of prevention of PTS. Until such trials are conducted or more clinical experience suggests the superiority of these evolving treatment modalities in acute DVT, it is important to continue to restrict aggressive endovascular interventions to situations in which compelling indications exist (*table 5*).

With respect to the patient characteristics, we need to know which patients benefit most from aggressive therapy. Perhaps the younger, healthier patient, who will face many years of decreased productivity if severe PTS develops, is the main candidate. In addition, young, healthy patients possibly have a decreased risk of bleeding related to thrombolysis.

Future research using randomised controlled studies should focus on the following key questions:

- Does thromboablative therapy improve long-term outcomes of DVT with a favourable risk-to-benefit ratio and, if so, which patients are most likely to benefit in the long term?
- What is the precise role of CDT or PMT in the treatment of VTE, particularly the use of a low-dose thrombolytic agent in conjunction with mechanical clot disruption to minimise bleeding in patients with high risk?

Table 4
Percutaneous mechanical thrombectomy for DVT

AUTHOR (YEAR)	N	MEAN FOLLOW-UP (MONTHS)	DEVICE	THROMBOLYTIC N	SIGNIFICANT/ RESOLUTION N (%)	PE	STENT	MAJOR BLEEDING N (%)	DEATH	PTS
Kasirajan (2001)	17	9	Angiojet	9	10 (59)	0	7	0	0	ND
Delomez* (2001)	18	29.6	Amplatz/-	0	15 (83)	0	6	0	1	1
Vedantham (2002)	28		**	28 UK/ rt-PA	17 (62)	0	18	3 (14)	0	ND
Vedantham (2004)	23	19.8	Helix	23 reteplase	19 (83)	0	23	1 (6)	0	2

*PE = pulmonary embolism; PTS = post-thrombotic syndrome; UK = urokinase; rt-PA = recombinant plasminogen activator; ND = not determined; *only mechanical treatment after failure of conventional heparin after 48 hours + cava filter, **different devices were used: Amplatz, Angiojet, Trerotola and Oasis.*

Table 5
Possible indications for interventional therapy on acute lower extremity DVT

Young or highly functional patients with iliofemoral DVT
Extensive thrombus burden
Extension to IVC (especially with floating IVC thrombus)
Associated findings of venous ischaemia
Phlegmasia cerulea dolens
High risk of fatal PE
Symptomatic IVC thrombosis after filter placement
Propagation of DVT despite conventional therapy
High likelihood of underlying anatomic abnormality (previous pelvic DVT, compression by pelvic tumour, May-Thurner syndrome)

According to the current data, thrombolytic treatment for DVT should not be applied except in extraordinary circumstances. First, the long-term effectiveness in terms of reducing PTS, although possible, remains uncertain. Second, the risks of thrombolytic therapy are high. Third, current conventional therapy is relatively inexpensive, convenient and safe.

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BOEKAANKONDIGING

Richtlijn Behandeling van tabaksverslaving

Met jaarlijks meer dan 20.000 doden door tabaksgebruik, is roken in Nederland een volksgezondheidsprobleem van de eerste orde. Dertig procent van de bevolking rookt nog. De winst van stoppen met roken is niet alleen voor de maatschappij als geheel, maar ook voor elke individuele roker, aanzienlijk. De meeste rokers blijken graag te willen stoppen. Velen hechten daarbij grote waarde aan advies van een medicus.

De richtlijn sluit aan op het principe van eenmalige en korte ondersteunende interventies en op het model van 'stages of change'. De minimale-interventiestrategie (MIS) kent in ons land als toegepaste methode een zekere traditie waar het gaat om het bieden van 'stoppen met roken'-adviezen: diverse beschikbare programma's zijn hierop gebaseerd. In de richtlijn wordt de MIS echter als een methode gezien en wordt een andere indeling gehanteerd dan in de traditie van de MIS. Een belangrijk uitgangspunt in richtlijnen voor de medische praktijk is dat optimaal gebruik wordt gemaakt van beschikbare voorzieningen. In deze richtlijn is dat ook het geval waar het gaat om een consistente motiverende interventie bij rokers. Een bijzonder punt in deze richtlijn is echter het positioneren van gespecialiseerde voorzieningen. Deze, in het Verenigd Koninkrijk en de Verenigde Staten bekende, voorzieningen zijn in ons land op beperkte schaal voorhanden. Met het lanceren van deze richtlijn wordt bepleit dat zulke faciliteiten op grotere schaal beschikbaar komen. Ondanks het beperkte wetenschappelijk bewijs wordt hiervoor een argumentatie gegeven. Daarmee zal het realiseren van de inspanning om via individuele interventies het tabaksgebruik terug te dringen, aan slagkracht winnen.

In de gezondheidszorg doen zich op grote schaal contacten met individuele rokers voor. In deze richtlijn worden die momenten als aanleiding beschouwd om stoppen met roken aan de orde te stellen. Voor de medische praktijk en de daarbij betrokken hulpverleners biedt deze richtlijn mogelijkheden om tabaksverslaving effectief te behandelen. Hoewel primaire preventie met name voor jongeren van groot belang is, komt in deze richtlijn alleen de behandeling van tabaksverslaving in de zorg aan de orde.

Richtlijn Behandeling van tabaksverslaving
(met samenvattingkaart)

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REVIEW

Falls and medications in the elderly

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INTRODUCTION

Falls are common in the elderly and contribute to morbidity and mortality. Elderly people are often on a variety of medications as well, and this suggests a causative relation between use of medicine and falls. However, the evidence available to support this assumed relationship is not very robust. In this article, we will discuss specifically the medications that are presumed to be associated with falls.
Falls in older people are a major public health problem with significant consequences for individuals, their families, and healthcare providers. The incidence of hip fractures increases with age. In the over 65 year olds, the rate of hospital admissions due to fractures from falls is increasing.[1] There has been a doubling of the hospital admission rate for patients >65 years with a hip fracture in the Netherlands during the last 20 years.[2-4] This has resulted in an enormous increase in the costs of intramural and extramural healthcare. In addition to an influence on morbidity and mortality, falls have a negative effect on daily life activities and quality of life. This is especially so when the fear of falling leads to avoidance behaviour, which promotes inactivity with a further deconditioning of musculoskeletal function, propensity to inactivity and social isolation, all facilitating new falls.[5]
In the elderly, falls represent a multifactorial problem which should be regarded as the result of complex interactions between intrinsic factors and factors relating to environment and the specific situation. Judicious application of medications that enhance the likelihood of falling probably contributes to prevention of an important cause of morbidity in the elderly.[6] Recent data from the Dutch Foundation for Pharmaceutical Statistics (SFK) have revealed that salicylates used as an antiplatelet agent, temazepam, furosemide and oxazepam (also see: www.sfk.nl) are among the medicines most frequently taken by elderly patients (>65 years).
Pathophysiology of orthostatic hypotension is discussed and changes in the pharmacokinetics and pharmocodynamics due to ageing are addressed. A focus will be on the evidence currently available on medication as a risk factor for the occurrence of dizziness and falls. Osteoporosis and effects of medications on reaction time are beyond the scope of this review.

DEFINING THE PROBLEM

For elderly people aged >65 years who live in the community, the risk of falling varies from 25 to 40% a year,[2,3,7,8] while for the institutionalised elderly this can be as high as 70%.[9] The incidence of falls increases with age and is greater in women.[10-12]
At least 5% of community-dwelling elderly >65 years will suffer from a fracture related to a fall. Especially fractures of the hip result in hospital admission[4] with a death rate within the following year of 20 to 30%.[13,15] The same percentage of elderly people is admitted to a nursing home because of remaining disability.[13,14]

PATHOPHYSIOLOGY OF ORTHOSTASIS

Normovolaemia may be defined as the effectively circulating volume of a healthy person in the supine position.[17] A change in posture to the upright position elicits a shift of

~300 to 800 ml of blood from the chest to the lower parts of the body. To maintain cardiac output, the consequent fall in ventricular filling volume must be met by continuous adjustment of arterial and venomotor tone and by regulating cardiac contractility and chronotropy.[18] Humans can stand upright for long periods of time. Their orthostatic circulatory adaptation is provided by the evolution of an effective set of neuromuscular and circulatory mechanisms that are largely involuntary or autonomic, aiming to preserve arterial pressure as the controlled variable, independent of gravity. The arterial baroreflex is the well-known example of short-term control acting within the single heartbeat, while the more slowly acting but extremely powerful humoral-cardiovascular-renal system secures body fluid control, provided the fluid intake is normal.[19,20]

Orthostatic stress affects cerebral perfusion pressure and the cerebral autoregulatory system aims to limit the postural reduction in perfusion of the brain. Nevertheless assumption of the sitting or standing position affects cerebral perfusion and regional cerebral oxygenation in healthy humans.[21-23]

Age-related changes

Although function and efficacy of cardiovascular reflex activity change with increasing age,[24,25] arterial pressure in the upright position is usually well maintained.[26] In addition, the magnitude of the blood volume declines with age but its possibly disadvantageous effects are offset at least in part by the concurrent decline in venous compliance limiting the volume of blood pooled. This explains the increased susceptibility of elderly patients for diuretic treatment interfering with the maintenance of blood volume and thus orthostatic tolerance.[27,28]

Postural stress affects cerebral oxygenation in the elderly[29] but it is as yet uncertain whether this is related to a decline in autoregulatory capacity.[30] Orthostatic tolerance in the elderly is reduced,[31] and blood pressure and cerebral perfusion are affected further for at least for ~45 to 60 minutes following a meal.[32-36] Postprandial hypotension is defined as a >20 mmHg postural drop in systolic blood pressure but this cut-off point should be regarded as less relevant with respect to the development of orthostatic symptoms.[16] Especially in elderly people with hypertension a limited reduction in blood pressure may already elicit symptoms of cerebral incompetence.[37] Following a meal, instead of resting, walking may benefit postprandial blood pressure and development of symptoms.[38] Moderate exercise training expands plasma volume and enhances leg muscle tone limiting orthostatic venous pooling and supporting orthostatic tolerance.[39] In the elderly the use of medicines and time of a meal may interfere with orthostatic tolerance in a complex way.

AGE-RELATED CHANGES OF PHARMACOKINETICS AND PHARMACODYNAMICS

In the elderly, the rate of absorption of most drugs administered orally is almost identical to that of younger people, but with ageing marked changes in body components affect the distribution. Body fat as a proportion of body weight increases by over 35% from the age of 20 to 70 years. There is a concurrent decrease in plasma volume of 8% with normal ageing; lean body mass and total body water decrease approximately 17%[40] with an increased rate of adverse effects of both lipophilic (for example diazepam: large volume of distribution) and hydrophilic medications (high plasma concentration). Also the metabolism of many medicines changes with ageing. Hepatic biotransformation is a prerequisite for drugs with limited renal clearance. There is a modest decrease in the efficiency of phase I reactions (oxidative and hydroxylation processes), reactions generally mediated by the mixed-function monooxygenase system (cytochrome P-450 system). In contrast, phase II reactions (by conjugation enzymes and transferases) are generally unaffected and in older *vs* younger patients drugs metabolised by phase II processes only are preferable. Drugs known to have a strong 'first pass' effect, such as metoclopramide and opiates, should be used in low doses. Renal drug excretion includes glomerular filtration, tubular secretion, and in a varying degree, tubular reabsorption as well. The half-life of a drug is directly related to the volume of distribution and inversely related to its clearance (metabolism and excretion). In the majority of elderly people renal function is diminished due to a reduction in both renal blood flow and number of functional nephrons with an increased half-life for drugs that depend on renal function for elimination.[41] Insight into the effects of ageing on pharmacodynamics, probably through disease-related changes in target organs, diminished reserve capacity and changes in receptor function of end organs, is limited.[42] As an example, the plasma concentration of diazepam required to achieve a certain level of sedation is much lower in the elderly than in subjects aged 30 to 50 years. An increased sensitivity has also been shown for opiates, anticholinergic and antihypertensive drugs and dopamine agonists. In contrast, the susceptibility of older *vs* younger patients for β-blockade and insulin[40] is reduced. From this viewpoint, data from literature concerning antipsychotics, (tri)cyclic antidepressants, anticonvulsive and cardiovascular medications are discussed.

MEDICAL CAUSES AND RISK FACTORS FOR DIZZINESS AND FALLS

Theoretically, randomised controlled trials are likely to provide the evidence to prove the causal relationship between medication use and falls. When addressing the

specific cause of falls, the rate of falls must be known both in the intervention and the control group but such evidence is only rarely available. Data on the relationship between drugs and falls are usually derived from observational studies, for instance from cohort or patient-controlled studies, rendering interpretation of results difficult.
The majority of studies and reports available suggest a relationship between number of medications and the risk of falls.[9,40,43-53] Also a recent change in dosage of drugs is associated with an increased risk of falls. The use of psychotropic medication is regarded as a risk factor for falls.[40,54,55] Psychoactive medication likely contributes to the occurrence of falls by affecting balance, partly because of the extrapyramidal side effects, dizziness and postural hypotension[56] in addition to a delayed reaction time, with a higher incidence if combinations of medications are used. A fall resulting in hospital admission in the elderly is likely to be regarded as a side effect of drug treatment.[57] The risk of falls in the elderly is increased with postural instability, regardless of the cause which can range from acute illness with fever and dehydration, the use of a specific drug affecting plasma volume or the reaction time to floor covering. The risk of a second fall within one year is increased especially in elderly individuals on benzodiazepines, neuroleptics or anticonvulsants.[58]
Tables 1 and *2* give the odds ratios of psychoactive agents and falls.

Table 1
Pooled OR for associations between use of various psychotropic medications from 40 nonrandomised controlled trial[46,63]

Benzodiazepines	OR 1.48 (95% CI 1.23-1.77)
Short-acting	OR 1.44 (95% CI 1.09-1.90)
Long-acting	OR 1.32 (95% CI 0.98-1.77)
Antidepressants	OR 1.66 (95% CI 1.38-2.00)
TCAs	OR 1.51 (95% CI 1.14-2.00)
SSRIs: low dose	OR 1.50 (95% CI 1.30-1.70)
high dose	OR 2.40 (95% CI 1.70-2.20)
Neuroleptics	OR 1.50 (95% CI 1.25-1.79)

OR = odds ratio; TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor.

Table 2
Psychotropic medication from nonrandomised controlled trials[46,63]

Benzodiazepines	
Short-acting	Lorazepam, oxazepam, temazepam, alprazolam, triazolam, bromazepam
Long-acting	Flurazepam, chlordiazepoxide, clonazepam, clorazepate, diazepam, prazepam
Antidepressants	Tricyclic antidepressants, selective serotonin reuptake inhibitors
Neuroleptics	Phenothiazines, butyrofenones

PROBLEMS CONCERNING RESEARCH OF FALLS AND MEDICATIONS

The available data from studies on risks of falls are difficult to compare because of the different definitions used for falls, the nature of the analysed risks, and the populations interrogated. Confounding by indication remains a most important consideration in pharmacoepidemiology.

Polypharmacy in the elderly is associated with an increased risk of falling, but it is equally likely to result from physical and mental frailty.[40,52,59,60] When interpreting epidemiological data it should be considered that in the majority of studies subjects in poor health were excluded from analysis, with gross underestimation of adverse drug events. In addition, the design of many studies focussed primarily on risk factors rather than on drugs.[40] Lumping together several groups of medications (excluding all psychoactive drugs) and poor recording of actual medication use at the time of the fall in many studies has limited the opportunity to identify specific drug classes. In addition, recall of falls and sample size to detect a moderate increase in drug risk is often insufficient, a methodological error common to many studies addressing adverse events of drugs.

Neuroleptics

All classes of neuroleptics increase the risk of falling, but through different mechanisms, including enhancement of extrapyramidal disturbance, syncope, α-blockade, sedation, postural hypotension and/or cognitive impairment.[61-63]

Tricyclic antidepressants and selective serotonin reuptake inhibitors

A prerequisite for appropriately identifying falls as adverse events from the use of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) is that a distinction is made between studies conducted in normal volunteers and those with symptoms of depression. When comparing drugs, the risk of falling relates to the sedative characteristics of the drug used. The risk of contracting a fractured hip is increased in elderly patients on tricyclic antidepressants, probably related both to the drug itself and to depression or confusion.[47] Confounding by indication can be of influence on the results of studies. In a recent study that corrected for indication by indication, an influence of prescription was no longer detected.[58]

In elderly patients on antidepressants, sedation with psychomotor retardation has been proposed as the most likely cause of falls.[64] When using TCAs, orthostatic hypotension (as a result of α-blockade) and cardiac arrhythmias are the most important factors contributing to falls. When using SSRIs, the risk is comparable[65-68] or even larger[58] than the risk with TCAs.

Polypharmacy in the elderly enhances the chance of interaction between drugs. Some SSRIs are strong inhibitors of isoforms of the cytochrome P450 system with important pharmacodynamic interactions.

No pharmacokinetic interaction was reported for dopamine agonists and SSRIs. On theoretical grounds interaction between ropinirol and fluvoxamine is likely because of the inhibition of metabolism of ropinirol through CYP1A2 by fluvoxamine.[62]

Benzodiazepines

In normal volunteers, benzodiazepines impair function in tests of postural sway, they delay reaction time, cause ataxia, reduce proprioception during the period corresponding to the drug's elimination half-life[69,40] but for the elderly the results are less uniform. Although in most studies a correlation between long half-life time and falls is confirmed, there is also evidence that benzodiazepines with a short half-life also lead to an increased risk of falls.[58,70] In one study the dose was more important than the half-life as such.[71] In elderly patients in general, side effects are more serious for each dose, regardless of the dosage, due to the mentioned changes in pharmocokinetics and pharmacodynamics.[72]

Anticonvulsants

The following side effects of anticonvulsants may be related to falls: sedation, dizziness and balance disturbances. In one study the likelihood of falling (≥1) for women taking anticonvulsants *vs* controls almost doubled, as did the rate of falling.[58]

Cardiovascular drugs

A relationship between usage of antihypertensive agents, diuretics or nitrates and the occurrence of falls in the elderly may seem plausible but it is hard to prove. In a meta-analysis of 29 nonrandomised studies addressing the relationship between cardiovascular drugs and falls in the elderly, a weak relationship could only be found for digitalis, type 1A antiarrhythmetic drugs and diuretics.

The evidence was, however, weak and based merely on observations with minimal correction for confounders, dosage or duration of treatment.[45] From a practical viewpoint, in the absence of firm evidence it is worthwhile to reconsider diuretic treatment in the elderly[73] although in a meta-analysis of randomised, cohort and patient-controlled studies no clear causal relationship between diuretic treatment and falls could be identified.[74] Polypharmacy is common and this is especially so in cardiovascular disease with chronic heart failure as an example, involving combination treatment with ACE inhibition, β-adrenergic blocking agents and often diuretics as well. The occurrence of orthostatic hypotension is a side effect of treatment aiming at left ventricular afterload reduction. Nevertheless a meta-analysis of 15 randomised trials regarding antihypertensive treatment in >21,000 subjects >60 years of age for at least a year did not reveal an increased fall rate.[75]

INTERVENTIONS

Reduction in total number of medications

When starting a drug or changing its dosage, one must decide whether it is clearly indicated and also if the benefits of the prescribed drug counterbalance its possible adverse effects, especially in the case of benzodiazepines, neuroleptics, antidepressants, anticonvulsants and cardiovascular medications. If a drug is indicated, it may be an option to choose a drug from a different class. In addition, in the elderly, periodical evaluation of the indications for drug treatment and/or consideration of dosage reduction is warranted. The ultimate goal is to optimalise daily functioning with a maximum of profit from drug treatment and a minimum of adverse effects, such as falls. In a single randomised double-blind trial addressing stopping of psychotropic drug treatment in institutionalised elderly patients >80 years, the risk of falling was reduced by 66%.[50] Reducing the total number (to less than four) of medications is a real option to reduce the risk of falls.[6,54,76,77]

Information and advice

When prescribing and delivering drugs it is important to inform the patient on the use of medication and their role in signalling side effects. The patient also has a responsibility concerning self-medication and reporting adverse events allowing timely intervention in limiting adverse events and interactions.

PERSPECTIVE

The relation between usage of drugs and falls has been studied in many trials, but the majority are retrospective, uncontrolled trials. From the data of studies available it is not yet possible to reveal a causal relationship for most drugs. Data from the majority of trials suggest that the use of drugs involves an increased risk of falling, especially in the frail geriatric patient on several drugs.

When prescribing a new medication in the older patient, the indication should be considered critically without withholding of treatment. When a decision to start treatment is made, one should 'start low, go slow', with explicit attention and active search to possible adverse events.

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Evaluation of cardiac ischaemia in cardiac asymptomatic newly diagnosed untreated patients with primary hypothyroidism

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ABSTRACT

Background: Hypothyroidism is regarded as a risk factor for coronary artery disease. Possible factors involved in this association are hyperlipidaemia and hypertension, both occurring with increased frequency in hypothyroid patients. The aim of our study was to evaluate signs/symptoms of cardiac ischaemia in untreated hypothyroid patients without angina pectoris, since this has never been performed before.

Methods: 51 consecutive cardiac asymptomatic patients (mean age 47, range 22 to 86 years) were studied by dobutamine stress echocardiography and bicycle ergometry.

Results: Mean values of body mass index, resting heart rate and blood pressure were 28.5 kg/m², 68 beats/min and 129/81 mmHg, respectively. Median TSH was 51.9 mU/l, mean FT4 7.3 ± 2.9 pmol/l (mean ± SD), TT3 1.6 ± 0.6 nmol/l and total cholesterol was 5.8 ± 1.6 mmol/l. None of the patients had symptoms of angina pectoris during dobutamine stress echocardiography or bicycle ergometry and no evidence of myocardial ischaemia was demonstrated. Exercise tolerance, assessed by dividing the maximum achieved workload by the target performance (depending on body height, sex and age), was diminished in 38% of patients, and significantly related to the degree of hypothyroidism.

Conclusion: No angina pectoris or cardiac ischaemia at exercise or stress was found in cardiac asymptomatic hypothyroid patients. The precise role of hypothyroidism as a risk factor for coronary artery disease should be further elucidated.

INTRODUCTION

Hypothyroidism and cardiac diseases have been associated for almost a century now. In 1918, Zondek introduced the term 'myxoedema heart', referring to pericardial effusion, ventricular dilatation and hypertrophy, and interstitial oedema with swelling of myocardial fibres.[1] In 1924, a first case of angina pectoris associated with myxoedema was reported.[2] Subsequently, several authors warned of the danger of initiating or aggravating angina pectoris, or even precipitating acute myocardial infarction, during thyroid replacement therapy in patients with both hypothyroidism and coronary artery disease.[3-6] Moreover, autopsies performed in hypothyroid patients before or during thyroid hormone therapy demonstrated coronary atherosclerosis and even fresh coronary occlusion.[3,6-8] Independently of age, sex and associated disorders, hypothyroidism was found to favour the development of coronary artery atherosclerosis.[7,8]

Several mechanisms might be involved in this historical association of hypothyroidism with ischaemic heart disease. Since both abnormalities of lipid metabolism (increased serum total cholesterol and low density lipoprotein cholesterol) and arterial hypertension occur with increased frequency in hypothyroidism, those two factors are regarded as possible causal factors.[9-15] Furthermore, it has been suggested that pathological immune reactivity in autoimmune thyroiditis, a common cause of thyroid failure, may be important in the above-referenced association.[16] As a consequence, most physicians are still hesitant about initiating the treatment of hypothyroid patients with a full dosage of thyroxine, even though Singer *et al.* suggest starting with a full replacement dosage of levothyroxine in those under the age of 50 without known

cardiac disease.[17] A systematic prospective study examining the prevalence of cardiac ischaemia before and during treatment, however, has never been performed. Most of the published studies on the association of hypothyroidism with coronary artery disease were retrospective, based only on the patient's history without the application of diagnostic tests, the numbers of the patients studied were often small and, particularly in earlier studies, patients were treated with desiccated thyroid containing differing amounts of triiodothyroxine.

The prevalence of coronary artery disease in untreated hypothyroid patients needs to be known to be able to determine the risk of angina pectoris developing during thyroid replacement therapy. By excluding patients with a known history of cardiac disease we were able to study only those patients in whom the development of angina pectoris due to coronary artery disease would be unexpected.

We therefore conducted a prospective study in which we determined the prevalence of cardiac ischaemia in untreated hypothyroid patients without symptoms of angina pectoris.

METHODS

Study population

All hypothyroid patients who presented to our hospital between September 1999 and August 2002 were screened for inclusion. Of these patients, only those with longstanding primary autoimmune hypothyroidism (TSH>4.2 mU/l and FT4<10 pmol/l) were included; the exact duration of hypothyroidism was, therefore, unknown. Subjects with a history of cardiac disease or taking cardiac medication were excluded from our study in order to evaluate the prevalence of ischaemia in asymptomatic patients and to avoid interference of the cardiac test results by the use of β-blockers and other cardiac medication. In total, we studied 51 consecutive patients with untreated hypothyroidism.

At diagnosis, before thyroid hormone replacement therapy was started, dobutamine stress echocardiography and bicycle ergometry were performed to identify signs and/or symptoms of myocardial ischaemia. In addition, an electrocardiogram was acquired, body height and weight were measured for calculation of body mass index (BMI, kg/m^2), blood pressure was measured in a supine position and free thyroxine (FT_4), total triiodothyroxine (TT_3), thyroid stimulatory hormone (TSH), total cholesterol and cholesterol subfractions and creatine phosphokinase (CK) were assayed at that time.

Clinical and biochemical characteristics of the study population were compared with those of 35 euthyroid, healthy control subjects chosen from hospital personnel and their relatives of comparable age who were not taking medication.

The study protocol was approved by the local medical ethics committee, and informed consent was obtained from each subject.

Assays

TSH plasma levels (reference range 0.4-4.2 mU/l), serum TT_3 levels (range 1.3-2.5 nmol/l) and FT_4 levels (range 10-23 pmol/l) were determined in a highly sensitive chemiluminescent enzyme immunoassay (ACS 180, Bayer Diagnostics, USA). Total cholesterol (range 2.5-6.5 mmol/l), cholesterol subfractions (high-density lipoprotein (HDL) cholesterol range 1.0-1.8 mmol/l, low-density lipoprotein (LDL) cholesterol 1.5-4.5 mmol/l, triglycerides (TG) 0.0-2.0 mmol/l) and creatine phosphokinase (CK 11-200 U/l) were measured with a Hitachi 911 (Japan).

Electrocardiography

All 12-lead electrocardiograms (ECGs) were analysed by one cardiologist and scored according to previously published criteria.[18]

Dobutamine stress echocardiography

This test was performed as previously described.[19]

In summary, a rest ECG and a two-dimensional echocardiogram were carried out and intravenous access was secured. Dobutamine was then administered intravenously by an infusion pump, starting at 10 μg/kg/min for three minutes, increasing by 10 μg/kg/min every three minutes up to a maximum of 40 μg/kg/min. In patients not achieving 85% of their estimated maximal heart rate (220 beats/min minus age for men, 200 beats/min minus age for women), atropine was administered on top of the maximal dosage of dobutamine, starting with 0.25 mg intravenously and repeated up to a maximum of 1.0 mg. Throughout dobutamine infusion, the ECG was continuously monitored and recorded at three-minute intervals. Blood pressure was measured and recorded by an automatic device every three minutes. Images were digitised in quad screen to allow later visual analysis of wall motion. Two experienced independent and blinded cardiologists analysed the echocardiogram. Myocardial ischaemia was defined as development of new or worsening of pre-existing wall motion abnormalities in at least two segments of the left ventricle.

Bicycle ergometry

A Lode bicycle ergometer was used. Workload was started at 30 watts with 20-watt increments every minute. A constant pedalling rate of 60 revs per minute was required and exercise was terminated if the patient was unable to maintain the requested cycling frequency. The ECG was continuously monitored and blood pressure was measured and recorded by an automatic device every two minutes. Ischaemia was defined as development of ST depression

of ≥0.1 mV during exercise, according to the criteria described by Roelandt *et al.*[20]
Bicycle ergometry can also be used to assess exercise tolerance, which could be a parameter of hypothyroid myopathy. Therefore, at the start a target performance was assessed for each patient, depending on body height, age and sex. Exercise tolerance was determined by dividing the maximum achieved workload per patient by his or her target performance. An exercise performance of less than 80% of the target performance is considered insufficient.

Statistical analysis
Data are expressed as mean ± standard deviation (SD). Statistical comparisons were performed by means of a two group unpaired Students t-test. A p value <0.05 was considered significant.

RESULTS

Seventy-four consecutive patients with primary hypothyroidism were screened for inclusion, of whom 23 patients were excluded. Clinical and biochemical characteristics of the remaining 51 patients and 35 control subjects are given in *table 1*. The resting blood pressure of the experimental patients was 129/81 ± 17/12 mmHg. The mean body mass index (BMI) was significantly higher in hypothyroid patients compared with euthyroid controls (28.5 ± 4.7 *vs* 24.1 (4.9 kg/m^2, p=0.0004), resting heart rate was lower (68 ± 13 *vs* 80 ± 9 beats/min, p=0.0001), HDL cholesterol was lower (1.4 ± 0.4 *vs* 1.5 ± 0.4 mmol/l, p<0.05), TG were higher (1.6 ± 1.0 *vs* 1.2 ± 0.6 mmol/l, p<0.05) and CK was significantly higher (296 ± 746 *vs* 72 ± 39 U/l, p=0.02).

Twenty-three patients were excluded: 14 for cardiovascular reasons, such as a history of cardiac disease (myocardial infarction: n=4; angina pectoris: n=5) and cardiac medication for longstanding hypertension (n=5). Other reasons were unwillingness to participate in the study (n=5), hypothyroidism due to postpartum thyroiditis (n=2), pregnancy (n=1) and myxoedema (pre)coma (n=1). Except for age (included *vs* excluded patients: 47 ± 17 *vs* 63 ± 18 years, p<0.001) and mean TSH level (100.8 ± 136.5 *vs* 51.9 ± 30.4 mU/l, p<0.01), clinical and biochemical characteristics did not differ significantly between the two groups.
Electrocardiographic abnormalities were observed in 24 patients: inversion of the T waves (n=4), ST-segment depression (n=1), sinus bradycardia (heart rate <60 beats/min, n=16), prolongation of the Q-T interval corrected for heart rate (QTc >0.43 msec, n=4) and low P wave, QRS and T wave amplitudes (n=5). Six of the electrocardiograms showed two different abnormalities.

Dobutamine stress echocardiography
The echocardiogram at rest showed normal wall motion and normal left ventricular function in all patients. During dobutamine and later atropine administration, none of the patients complained of angina pectoris and none demonstrated wall motion abnormalities signifying myocardial ischaemia. This test is not designed for the evaluation of diastolic function.

Bicycle ergometry
As with dobutamine stress echocardiography, none of the patients had symptoms of angina pectoris during bicycle ergometry and no ischaemia was demonstrated. No serious arrhythmias occurred.

Table 1
Clinical and biochemical characteristics of the included patients and controls

	INCLUDED	CONTROLS	P VALUE
Number	51	35	
Male/female	12/39	4/31	
Age (years)	47 ± 17	50 ± 12	NS
BMI (kg/m^2)	28.5 ± 4.7	24.1 ± 4.9	0.0004
Heart rate (beats/min)	68 ± 13	80 ± 9	0.0001
TSH (mU/l)	100.8 ± 136.5	2.3 ± 1.1	<0.0001
FT_4 (pmol/l)	7.3 ± 2.9	13.2 ± 2.1	<0.0001
TT_3 (nmol/l)	1.6 ± 0.6	2.0 ± 0.6	0.002
Total cholesterol (mmol/l)	5.8 ± 1.6	5.7 ± 1.0	NS
HDL cholesterol (mmol/l)	1.4 ± 0.4	1.5 ± 0.4	<0.05
LDL cholesterol (mmol/l)	3.7 ± 1.5	3.8 ± 1.1	NS
Triglycerides (mmol/l)	1.6 ± 1.0	1.2 ± 0.6	<0.05
CK (U/l)	296 ± 746	72.3 ± 38.7	0.02

Data as mean ± SD.

Exercise tolerance was insufficient in 38% of patients (performance of 77 ± 8% of target) and normal in 62% of patients (performance 110 ± 13% of target). The mean TSH levels of the patients performing insufficiently were higher than in those with an exercise performance that was normal according to body height, sex and age: 154.3 mU/l *vs* 70.2 mU/l ($p<0.05$, *table 2*). FT_4 was lower in the group with reduced exercise tolerance: 6.4 pmol/l *vs* 7.9 pmol/l ($p<0.05$). Median CK did not differ significantly between both groups.

DISCUSSION

Our study clearly showed that no cardiac ischaemia was demonstrated in 51 consecutive patients with untreated primary hypothyroidism without previous cardiac symptoms. Secondly, bicycle ergometry showed that 38% of patients performed insufficiently, indicating a significant inter-relationship between exercise performance and degree of hypothyroidism. This might in part be explained by impaired cardiac performance with low cardiac output, caused by bradycardia, a decrease in ventricular filling and a decrease in cardiac contractility.[21,22] Although cardiac output was not measured in our patients the absence of impaired left ventricular function makes this a very improbable explanation. Moreover, heart rate did not differ significantly between patients with normal or impaired exercise performance. Another explanation might be the existence of hypothyroid striated muscle myopathy,[23,24] supported by the finding of elevated serum CK in our patients. However, median CK levels did not differ significantly between patients with normal or impaired exercise performance. Finally, we observed electrocardiographic abnormalities in almost half of the included patients. It should be stressed, however, that the resting ECG is not a diagnostic tool for demonstrating cardiac ischaemia. Electrocardiographic abnormalities that are frequently observed in patients with hypothyroidism are sinus bradycardia (heart rate <60 beats/min, 31% of patients in this study), prolongation of Q-T interval (8% in this study) and abnormalities associated with pericardial effusion: flattening or inversion of the T waves (8% in this study) and low P wave, QRS and T wave amplitudes (10% in this study).[14,15] Obviously, these changes also occur when pericardial effusion is absent, since none of our patients had pericardial effusion.

Some possible limitations to our study should be mentioned. First, the average age of included patients is relatively low. An explanation for this is that we excluded patients with cardiac history or symptoms who were relatively older. However, the included patients did represent all ages (range 22 to 86 years, median 46 years). Second, bicycle ergometry may have limited sensibility and specificity for the presence of coronary artery disease: 55 to 70% and 85 to 95%, respectively,[25] with the lowest sensitivity in young women. However, an advantage of this test is that we were also able to assess exercise tolerance, something that has never been done before in untreated hypothyroid patients. Dobutamine stress echocardiography is the most specific noninvasive test for assessing coronary artery disease, with sensitivity and specificity of 80 and 84%, respectively.[19] Third, in patients who performed insufficiently during bicycle ergometry, evaluation of ischaemia may be suboptimal. However, dobutamine stress echocardiography with achievement of target heart rate was performed in these patients and did not show ischaemia. Finally, the included patients did not have hypertension and dyslipidaemia. This might be caused by the fact that nowadays hypothyroidism is often diagnosed at an early stage due to more frequent testing of serum TSH.

While in our study no ischaemia was demonstrated, earlier studies have repeatedly demonstrated the association of hypothyroidism with coronary artery disease, even in previously cardiac asymptomatic patients, and of hormone replacement therapy with angina pectoris.[1-9,15,26-27] However, a retrospectively reviewed Mayo Clinic series of

Table 2
TSH and FT4 in patients with insufficient and normal exercise performance

	INSUFFICIENT	NORMAL	P VALUE
Number	19	31	
Male/female	8/11	4/27	
Ever smokers	8	8	
TSH (mU/l)	154.3 ± 202.6	70.2 ± 58.8	0.047
FT_4 (pmol/l)	6.4 ± 3.2	7.9 ± 2.6	0.045
TT_3 (nmol/l)	1.3 ± 0.7	1.6 ± 0.5	NS
Systolic BP (mmHg)	124 ± 15	132 ± 17	0.046
Diastolic BP (mmHg)	80 ± 11	80 ± 12	NS
Heart rate (beats/min)	69 ± 11	67 ± 14	NS

Data as mean ± SD.

over 1500 patients with myxoedema shows that angina pectoris and myocardial infarction are rather infrequent among hypothyroid patients: just 4% had angina pectoris before thyroid replacement therapy was started and 2% of cardiac asymptomatic patients developed angina pectoris after treatment had begun. Thirty-eight percent of patients with angina pectoris before initiating thyroid hormone replacement were even reported to improve.[6] This may be explained by the fact that thyroid hormone replacement improves myocardial oxygen consumption.[28] Most of the above-mentioned studies on hypothyroidism and coronary artery disease, however, can be criticised for being either retrospective or uncontrolled, for small sample sizes or for using desiccated thyroid containing differing amounts of levothyroxine and triiodothyroxine. Patients are now treated by L-T_4 only: as this first has to be converted by the liver into T_3 by type I deiodinase, the heart is probably protected against high elevations of plasma T_3 levels. A systematic consecutive study on this association has never been reported.

Interestingly, few studies have been published in which dobutamine stress echocardiography is performed in asymptomatic patients with other known risk factors for coronary artery disease and no studies in hypothyroid patients have been performed before. We found one study in which dobutamine stress echocardiography was performed in asymptomatic diabetic patients having at least three added risk factors but without rest ECG abnormalities. The authors concluded that asymptomatic coronary artery disease is common in diabetes associated with other risk factors. Moreover, dobutamine stress echocardiography appeared useful in its detection with a predictive positive value of 69%.[29] We did not find any studies of cardiac asymptomatic subjects with hyperlipidaemia and no studies of dobutamine stress echocardiography in cardiac asymptomatic subjects without risk factors for coronary artery disease.

Further research should include a prospective study in which development of angina pectoris during thyroid replacement therapy is monitored, as this could have important implications for future therapy. It is imaginable that patients who are treated initially with a higher dose of thyroxine will be euthyroid, and might feel better, much sooner than patients treated according to the present principle of starting low and increasing slow. Moreover, elevated arterial blood pressure and high serum cholesterol, both predisposing factors for coronary artery disease, might decrease sooner.

CONCLUSION

In conclusion, our data show that none of the cardiac asymptomatic patients with untreated hypothyroidism showed angina pectoris during stress testing and that no signs of ischaemia were found in these patients. The precise role of hypothyroidism as a risk factor for coronary artery disease should further be elucidated.

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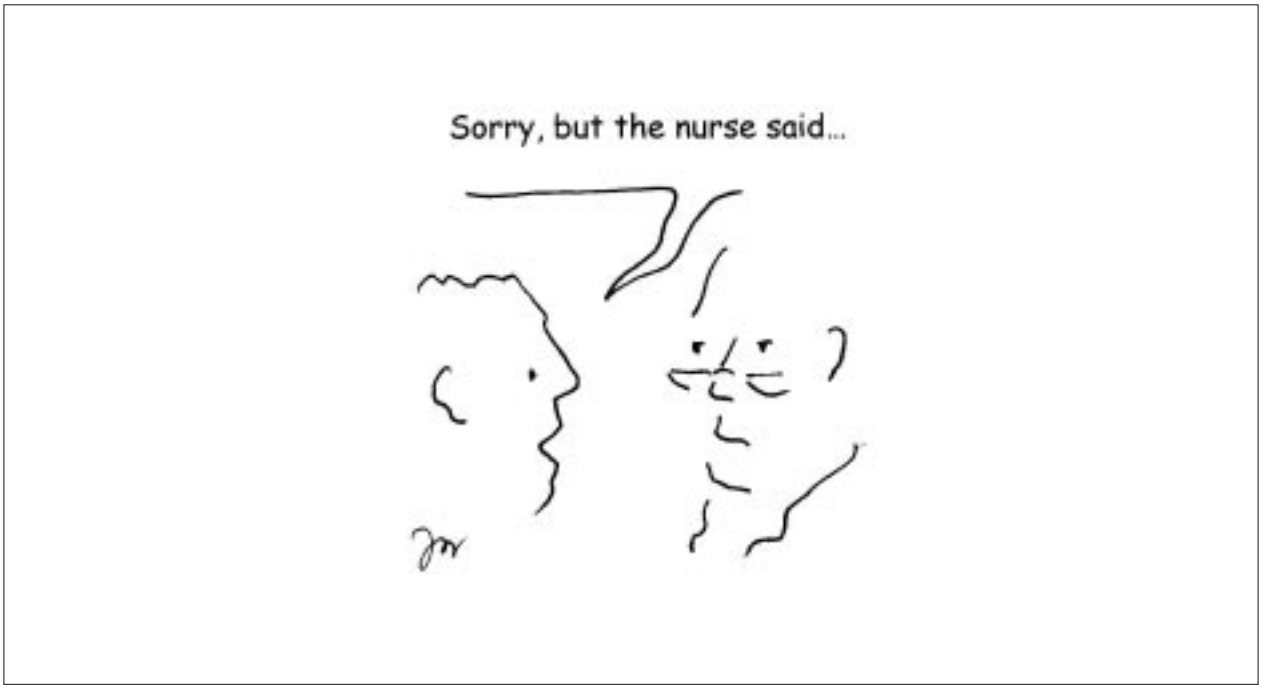

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Shared care with task delegation to nurses for type 2 diabetes: prospective observational study

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ABSTRACT

Background: To study the effects of two different structured shared care interventions, tailored to local needs and resources, in an unselected patient population with type 2 diabetes mellitus.

Methods: A three-year prospective observational study of two interventions and standard care. The interventions involved extensive (A) or limited (B) task delegation from general practitioners to hospital-liaised nurses specialised in diabetes and included a diabetes register, structured recall, facilitated generalist-specialist communication, audit and feedback, patient-specific reminders, and emphasised patient education. The target population consisted of 2660 patients with type 2 diabetes treated in the primary care setting. Patients who were terminally ill or who had been diagnosed with dementia were excluded from the study.

Results: The participation rates were high (90%) for patients, and none of the 64 GPs discontinued their participation in the study. Longitudinal analyses showed significant improvements in quality indicators for both intervention groups (process parameters and achieved target values on the individual patient level); in standard care, performance remained stable or deteriorated. Both patients and caregivers appeared satisfied with the project.

Conclusion: This study shows that structured shared care with task delegation to nurses, targeted at a large unselected general practice population, is feasible and can positively affect the quality of care for patients with type 2 diabetes.

INTRODUCTION

Type 2 diabetes mellitus (type 2 DM) is a chronic disease, which leads to considerable morbidity and premature mortality.[1,2] The prevalence of type 2 DM is high and is increasing.[3] Since most patients with diabetes die from complications of atherosclerosis, they should receive intensive preventive interventions to reduce their cardiovascular risk.[4] Guidelines for clinical practice have been developed in many countries to optimise diabetes care.[5,6] However, the implementation of these guidelines has not been straightforward.[7,8] There are many reasons for this, including a lack of time, recall facilities and diabetes registers, staffing problems, poor quality of documentation, the unavailability of qualified nurses, problems with patient compliance, inadequate reimbursement, lack of physician consultative assistance, and long waiting lists for ophthalmologists.[9,10]

As in other countries, in the Netherlands the care for type 2 DM patients is concentrated in the primary care setting,[6,11] and there is a growing shortage of primary healthcare providers.[12,13]

Structured shared care can partially resolve the aforementioned problems and may also improve the quality of care for patients with diabetes.[14] Multifaceted complex interventions which target different barriers preventing change are the most effective. Successful interventions include applying organisational strategies that increase structured recall, protecting time which has been reserved for diabetes care, using multifaceted professional interventions, facilitating generalist-specialist communication, delegating tasks to practice assistants or nurses and using specialist diabetes nurse facilitators. Nurses can play an important role in encouraging compliance and educating

patients. In certain situations, they can even replace physicians in delivering many aspects of diabetes care.[9,10,14-16]

Previous studies on diabetes care in general practice have tended to include highly selected populations of practitioners and patients.

Our aim was to study the effects of two different forms of structured shared care, tailored to local needs and resources, and of standard care in an unselected type 2 DM patient population in a prospective observational study.

MATERIALS AND METHODS

Study design

The Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC) study investigated the effects of a shared care project for type 2 DM. In the Netherlands, general practitioners (GPs) collaborate in GP working groups. A GP working group consists of several GPs who practice in the same area or town, and cover for each other in the delivery of medical services during out-of-office hours. Eight GP working groups (64 GPs) in the east of the Netherlands agreed to participate in the study. Three GPs were excluded from the study, two because they had recently started a new practice and one due to retirement. For pragmatic reasons, allocation to the two intervention groups and to the standard care group was assigned according to the preference of the GP working groups as a whole. As Greenhalgh mentioned, it is important to recognise that the different ways in which GPs organise their diabetes care and in which they interface with specialist services is a function of both the particular needs of their practice populations and their individual skills and confidence.[14] Moreover, for interventions to work, the methods must be acceptable to the target groups.[17]

The 32 GPs who participated in intervention A received extensive support from nurses specialised in diabetes (DSNs) who were hospital based, but who worked for the project in the primary care setting. The second group (intervention B, 21 GPs) received limited support from DSNs, and the third group (intervention C, 8 GPs), the standard care group, delivered standard care and received no extra support. In this project, 1.6 full-time equivalent DSNs were employed.

INTERVENTIONS

Extensive support (intervention A) means that DSNs, rather than the GPs, performed the annual examination according to the national guidelines of the Dutch College of General Practitioners for all the DM patients treated in the primary healthcare setting. The GPs remained responsible for the check-ups that should take place every three months. On top of this, the DSNs gave one-on-one education, tailored to the needs of the individual patients. Fundus photography[18] was integrated into the consultation as well, where normally each patient would have been referred to an ophthalmologist. If necessary (according to retinal photography results, or in the case of a newly diagnosed diabetes) a referral to the ophthalmologist was arranged by the DSN. The appointments with the DSNs took place outside the hospital in the primary healthcare setting in the village or city where the patient lived. Any patient who missed his or her appointment was rescheduled. Patients who were housebound with serious comorbidity were visited at home. A comprehensive structured report of the results was sent to the GP within three weeks.

If necessary, the results were accompanied by recommendations from the DSN concerning referrals to a dietician, chiropodist, and/or podiatrist, and by a recommendation from an internist concerning treatment (according to the guidelines). This process allowed the GPs to dedicate their consultation time to discussing the results with the patient in detail, and to decide how to act upon them. The GPs kept the full responsibility for the care of the patients and were not under any obligation to follow the recommendations they were given. A second part of the extensive support structure was the possibility of sending individual patients directly to the DSN for an on-demand consultation within the primary healthcare setting (without, as in standard care, a formal referral to secondary care). Possible reasons for requesting such a consultation could be for patient education, instruction on self-monitoring, or instruction on insulin injection. The GPs were responsible for determining the initial insulin dosages and for making any dosage changes.

The only extraneous support the GPs in intervention group B received was having direct access to on-demand consultations with the DSN, without the need for a formal referral to secondary care. They performed the annual and three-monthly check-ups themselves, including making any necessary referrals to the ophthalmologist.

In the standard care group (8 GPs), patient care was delivered as usual, with no extra support. Consultation with a DSN was only possible through a formal referral to the internist in the secondary healthcare setting.

All participating GPs received one-time feedback about their baseline performance, which was discussed within the GP working group in the presence of an internist.

Patients

The target population consisted of patients with type 2 diabetes who were being treated in the primary care setting, and the aim was to have an unselected population. Virtually all citizens of the Netherlands are registered with a GP. Annually, the GPs provided lists with the

names of all the patients who were known to have type 2 diabetes, as defined by the guidelines of the Dutch College of General Practitioners.[6] Patients with type 1 diabetes were excluded. Type 1 diabetes was defined by age at diagnosis <40 years and a requirement for insulin within one month of diagnosis. A total of 155,774 persons were registered with the 61 participating GPs, 3362 of whom had been diagnosed with type 2 diabetes mellitus. Patients were only excluded if they were being treated in secondary care by an internist, if they were terminally ill, or if they had been diagnosed with severe dementia.

Data collection

We collected data on all the eligible patients with type 2 DM who were registered with and were treated by the 61 GPs, during the three consecutive years from 1998 to 2000. The data were collected annually for all patients from the (electronic and/or paper) patient records in the general practice (including correspondence with specialists) by the principal investigator of the study. Additionally, data were collected by the investigator from the reports on the consultations by the DSNs in the intervention groups A and B.

The data were collected on full medical history, microvascular and macrovascular complications, diabetes and other medication(s), referrals for ophthalmological examination, measurements of blood pressure and weight, foot examination, smoking status, and laboratory measurements: HbA_{1c}, total cholesterol, HDL cholesterol, triglycerides, creatinine, microalbuminuria, and albumin-creatinine ratio in urine (reference value for HbA_{1c} 4.0 to 6.0%). The blood pressure was measured by the DSN in intervention group A, and by the GP in intervention group B and in the standard care group. The blood pressure was measured twice with a Welch Allyn Sphygmomanometer in the supine position after at least five minutes of rest. Renal clearance was calculated by the Cockroft and Gault formula.[19] The data on patient and provider satisfaction were collected by asking the GP 'How do you judge the shared care project?' and 'How do your patients judge the shared care project?' The Medical Ethics Committee of the Isala Clinics (formerly Weezenlanden Hospital) approved this study.

Outcome measurements

The effects of the interventions were measured by changes in three quality indicators. We studied (1) process control (the percentage of patients with examinations and measurements performed according to the guidelines), and (2) outcome control (the percentage of patients who achieved target values: HbA1c <7.0%, blood pressure <150/85 mmHg, total cholesterol <5 mmol/l). Based on available data, expressing the number of patients known to have achieved target values as a percentage of the total target population results in a quality indicator (3) that combines process and outcome control. The feasibility of the interventions was evaluated based on the participation rates of the patients and the GPs and patient and provider satisfaction.

Analysis

Statistical analyses were performed using SPSS for Windows. For baseline cross-sectional analyses we used Student's T-test, and the One-way Anova for variables with a normal distribution, Mann-Whitney-U test for non-normal variables, and the χ^2 test for categorical variables. For longitudinal analyses we performed an 'intention-to-treat analysis' and used the McNemar method. The different groups were not directly compared with each other because of the possible bias resulting from the non-randomised design.

RESULTS

The prevalence of diabetes in the study area was representative for a larger area, and the size of the practice population and the percentage of GPs working in solo-practices were similarly representative for the population of the Netherlands. None of the GPs discontinued their participation in the study.

Among the 2660 patients with type 2 diabetes treated in the primary care setting (*figure 1*), 174 (6.5%) were excluded by their GPs for reasons of terminal illness or dementia. Altogether, 2486 patients were eligible for the study: 1244 were assigned to intervention group A, 842 to group B, and 400 to the standard care group.

Baseline data are shown in *table 1*. The three groups differed significantly at baseline with respect to age, diabetes duration, glycaemic control, cardiovascular risk factors, and treatment. Patients who were excluded were older (77.3 *vs* 68.4 years), had more cerebrovascular complications (23 *vs* 11%), used significantly less antidiabetic, antihypertensive, and lipid-lowering medication, and had their eyes (26 *vs* 55%) and feet (22 *vs* 36%) examined less frequently compared with participants.

Out of 2486 patients, 2048 (82%) were available for follow-up after two years: 217 (8.7%) patients died, 154 (6.2%) were referred to an internist, 66 (2.7%) moved, and two patients were lost to follow-up. The referral percentages to secondary care were 7% for group A, 4% for B, and 9% for the standard care group. The follow-up for the different groups was 77% for intervention A, 88% for intervention B and 79% for the standard care group. In intervention A, 1121 (90.1%) of patients responded to the invitation for a consultation with the DSN at least twice during the three years of the project, and 33 (2.7%) were excluded by the GP after initially participating.

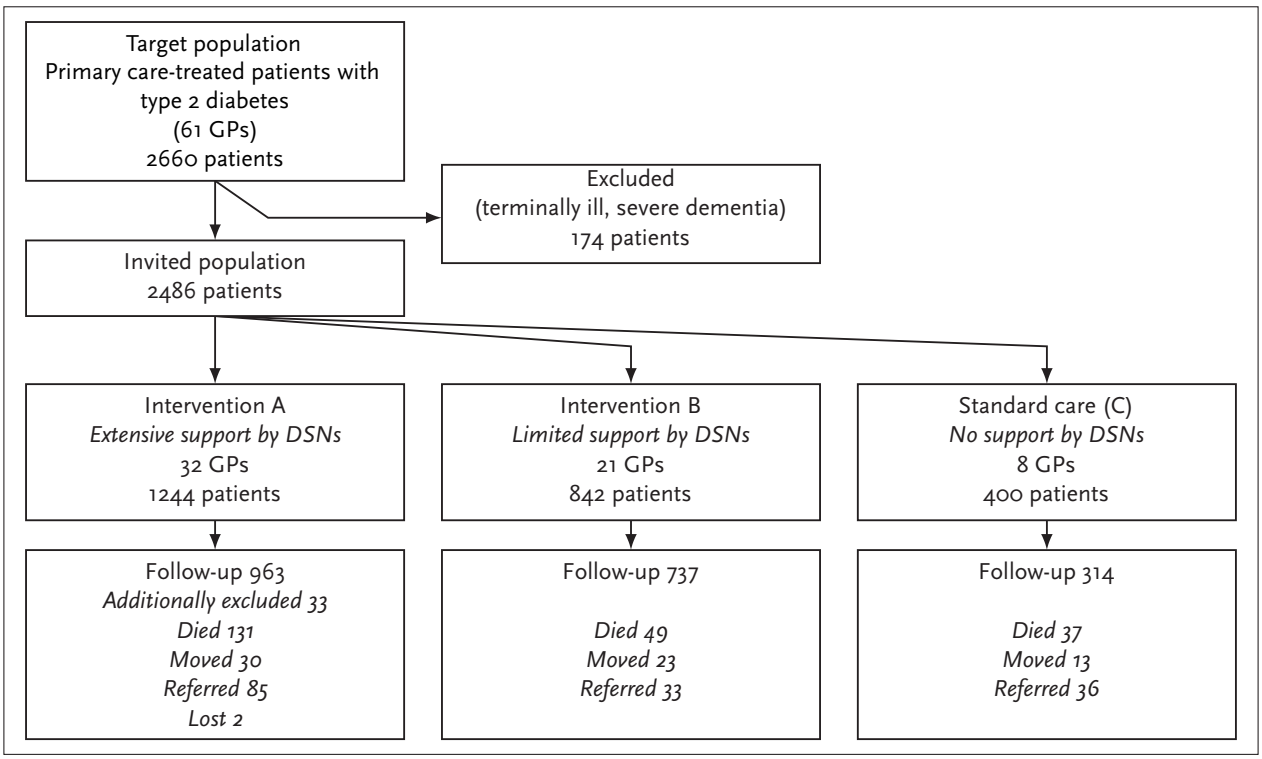

Figure 1

Selection of patients with type 2 diabetes treated in primary care, assignment to the interventions in the ZODIAC study, and follow-up between 1998 and 2001

Table 1

Baseline data from patients with type 2 diabetes treated in primary care in intervention groups A and B, and standard care group C (means or percentages), 1998/1999

	INTERVENTION GROUP		STANDARD CARE		
	A	B	C	TOTAL	P VALUE*
Practice characteristics					
Gender GPs male (%)	88	85	100	89	0.52
Practice size	2612	2523	2732	2598	0.51
Prevalence DM (%)	1.9	2.3	2.4	2.1	0.09
Patients (N)	1127	842	400	2369	
Gender female (%)	58	54	60	57	0.07
Age (years)	68.7	67.3	70.3	68,5	<0.001
Diabetes duration (years)	7.7	6.7	6.5	7.2	0.002
HbA_{1c} (%)	7.5	7.3	7.3	7.4	0.01
BMI (kg/m^2)	28.9	28.0	26.7	28.8	0.01
Systolic blood pressure(mmHg)	155	150	152	153	<0.001
Diastolic blood pressure (mmHg)	84	83	84	84	0.15
Total cholesterol (mmol/l)	5.7	5.5	5.9	5.7	0.003
Total cholesterol/HDL ratio	5.3	5.2	5.0	5.2	0.25
Diabetes treatment					
Diet (%)	13	20	10	15	<0.001
Oral agent (%)	70	64	75	69	
Insulin (%)	14	12	12	13	
Insulin and oral agent (%)	2	5	3	3	

**Single test for statistically significant differences between A, B, and C.*

The opportunity to consult with a DSN on-demand was not frequently used. The reasons for these consultations were, in the majority of cases, for support with respect to education and instruction of insulin therapy within the primary care setting: 27/47 (57%) for group A and 11/19 (58%) for group B.

The effects of the interventions are shown in *tables 2* and *3*. *Table 2* shows the change in process control. Performance significantly improved with respect to process parameters for both interventions A (extensive support by DSNs) and B (limited support by DSNs): at two-year follow-up, all examinations and measurements were performed more frequently for group A, and most for B. In intervention A, where the DSN is responsible for the annual check-up, the performance was very high, ranging from 84 to 90%; for intervention B this ranged from 18 to 85%. In the standard care group, the performance regarding process parameters remained stable or decreased, ranging from 2 to 72% for the various parameters after two years of follow-up. *Table 3* shows the change in outcome control:

Table 2

Performance with respect to process control in the treatment of patients with type 2 diabetes treated in primary care in intervention groups A and B, and standard care group C in 1998/1999 and 2000/2001

		BASELINE (%)	FOLLOW-UP (%)	P VALUE	DIRECTION OF SIGNIFICANT CHANGE
Foot examination	A	44	87	<0.001	↑
	B	31	41	<0.001	↑
	C	16	11	0.11	-
Eye examination	A	48	84	<0.001	↑
	B	57	67	<0.001	↑
	C	41	53	0.001	↑
HbA_{1c}	A	57	89	<0.001	↑
	B	67	75	<0.001	↑
	C	62	63	0.91	-
Blood pressure	A	76	88	<0.001	↑
	B	89	85	0.03	↓
	C	78	72	0.03	↓
Total cholesterol	A	46	89	<0.001	↑
	B	59	63	0.06	-
	C	48	39	0.008	↓
Creatinine	A	54	89	<0.001	↑
	B	63	74	<0.001	↑
	C	60	63	0.33	-
Body mass index	A	0.3	88	<0.001	↑
	B	0.3	18	<0.001	↑
	C	0.6	2	0.45	-
Smoking status known	A	5	90	<0.001	↑
	B	25	41	0.001	↑
	C	7	11	0.001	↑

Table 3

Quality indicators for the treatment of patients with type 2 diabetes treated in primary care in intervention groups A and B, and standard care group C in 1998/1999 and 2000/2001

		PROCESS CONTROL	OUTCOME CONTROL				PROCESS AND OUTCOME CONTROL COMBINED
	GROUP	(%)	BASELINE (%)	FOLLOW-UP (%)	P VALUE	DIRECTION OF CHANGE[#]	(%)[*]
HbA_{1c} ≤7.0%	A	89	43	42	0.76	-	37 (350/963)
	B	75	46	48	1.0	-	36 (264/737)
	C	63	50	42	0.03	↓	27 (84/314)
Blood pressure ≤150/85 mmHg	A	88	40	52	<0.001	↑	46 (439/963)
	B	85	47	51	0.02	↑	44 (321/737)
	C	72	43	42	0.92	-	30 (95/314)
Total cholesterol ≤5 mmol/l	A	89	28	40	<0.001	↑	35 (341/963)
	B	63	33	49	<0.001	↑	31 (227/737)
	C	39	26	26	0.27	-	10 (32/314)

[*]*Known achieved target values in the total population (%);* [#]*p<0.05.*

performance regarding the percentage of patients who achieved target values for the different groups. The percentage of patients with good glycaemic regulation remained stable in intervention groups A and B, and decreased in the standard care group. For both blood pressure and hypercholesterolaemia, outcome control improved in intervention groups A and B, while there was no change in the standard care group. Based on the available data, expressing the number of patients known to have achieved target values as a percentage of the total target population results in a quality indicator that combines process and outcome control. It appears that the performance for this quality indicator was 35 to 46% for intervention A, 31 to 44% for intervention B, and 10 to 30% for the standard care group.

The GPs rated the project as good in 70 and 69% of cases and adequate in 30 and 25% of cases in interventions A and B, respectively; the patients were satisfied in 81% of cases according to their GPs. There was no mention of dissatisfaction.

DISCUSSION

In this study, examining two interventions with structured shared care and task delegation, which was targeted at an unselected group of patients with type 2 diabetes treated in a primary care setting, we found improvements in process and outcome control. Performance for process parameters increased for both interventions, as did the percentage of achieved target values on the individual patient level for blood pressure and total cholesterol, but not for blood glucose control. In contrast, the standard care group showed minimal improvements, and even some deterioration. The patient participation rate remained high throughout the study, and none of the GPs discontinued participation.

Strengths and limitations

A strong point of this study is that the results may, for the most part, be generalised to similar patient populations. We studied a highly unselected patient population, unlike many of the previous studies on this topic. The quality of care improved even though changes are difficult to effect in busy primary care environments.[20] The interventions used in this study may be used in other primary care settings, provided the same exclusion criteria are applied. Excluding those terminally ill or having dementia seems realistic from a clinical point of view: intensive therapy is either not useful for prevention of long-term complications or not possible.[21]

A limitation of our study is the nonrandomised design. To study how evidence and guidelines may be translated into daily practice, flexibility is necessary to deal with pragmatic issues; rigorous nonrandomised study designs including quasi-experimental, time series and observational studies are sometimes more appropriate.[22] We chose, for pragmatic reasons, to assign the patients to the intervention groups according to the preferences of the GP working groups. The effects of the interventions may have been overestimated as a consequence of the design,[23] and baseline values were not comparable for the three groups analysed. Direct comparison would consequently be difficult to interpret. We therefore decided to limit our analysis to independent descriptions of the three intervention groups, and focussed on the quality indicators at the individual patient level instead of on group means. At the same time, there was a difference in the amount of available data: in group A the data collected during consultations with the patients by the DSNs were nearly complete. In groups B and C, however, the data were collected from the GPs' patient records, where the availability of data was not optimal. Obtaining data provided from medical records can lead to underreporting of care delivered.[24] However, although the same lack of documentation has been found by others,[20,25] and intermediate outcomes may not be different for the patients concerned,[25] the negligent recording of risk factors reflects suboptimal care, because opportunities to detect increased risk and therefore to start treatment are missed. Moreover, the quality of care delivered lacks transparency.

Comparison with other studies

With intervention A (extensive support by DSNs) a large increase was found with respect to process control, with an overall high performance rate between 84 and 90%, which is higher than that found in another recent study (41 to 80%).[25] This appears to be a direct effect of the central role of the DSNs who were responsible for performing the annual check-up. For intervention B (limited support by DSNs), process control improved as well, and was comparable with, or higher than (but still suboptimal) the findings reported by Goudswaard *et al.*[25] The standard care group showed few improvements, and even some deterioration. Renders *et al.* reported a similar finding for their reference group.[26]

For outcome control (achieved target values), in both intervention groups the percentage of patients achieving target values increased for blood pressure regulation and lipid control. Although difficult to compare, other intervention studies with a central role for DSNs showed improvement in blood pressure and/or lipid profile as well,[27-29] whereas programmes without a central role for DSNs found no (significant) positive effect on these outcomes.[26,30] In the standard care group no changes in outcome control for blood pressure or hypercholesterolaemia were found.

In the intervention groups we did not find an increase in the percentage of patients with good glycaemic regulation, whereas other intervention programmes did.[27,29-32] The percentage of patients with an HbA_{1c} <7 is comparable or somewhat lower compared with that found by others.[26,30,32] An explanation for the lack of improvement may be that the baseline HbA_{1c} was already quite acceptable in this unselected population, which may have left little room for improvement (ceiling effect).[33] The GPs in all three participating groups treat a higher percentage (80%) of the total diabetic population in primary care than in most other programmes (61 to 75%),[26,34,35] probably also including a higher percentage of patients who are difficult to treat. Since metabolic control tends to deteriorate with the duration of the disease,[36] keeping glycaemic control stable could be seen as a positive effect of the interventions. In the standard care group, the percentage of patients with good glycaemic regulation decreased, which was also reported by De Sonnaville *et al.* for their control group.[30] Using a quality indicator that combines process and outcome control may be a simple and transparent method to indicate the quality of care delivered, enabling benchmarking of performance at the level of the individual health care providers or teams.

In intervention group A, 9.9% of patients did not visit the DSN in either one of the three project years. This percentage seems acceptable as it is within the variance (0 to 17%) that is mentioned in a Dutch literature study into diabetes patients not showing up within a period of 6 to 13 months.[37] Reasons mentioned by patients varied between 'just don't want to' and 'long-term admittance to the hospital' or 'partner to ill' or 'family problems'. Many patients who could not participate in one year resumed participation in the next year.

The follow-up period may have been too short to show all the potential positive effects, since the GPs only started to make more use of on-demand consultations after two years. We expect that the intervention groups and the standard care group will diverge further with respect to the quality of care as, in intervention group A, the recommendations from the internists become increasingly stringent and extensive at the GPs' request. Moreover, we are currently seeing a large annual increase in on-demand consultations in intervention groups A and B.

Implications

Abnormal but unrecorded values deprive the GP of possible indications for starting or adjusting treatment, and may therefore hamper the achievement of optimal diabetes care at the individual patient level. Moreover, unrecorded values limit the transparency of the care delivered. In other healthcare settings, quality indicators have yet to be included in the assessment of the quality of diabetes care.[38] Although there have been proposals,[39,40] in the Netherlands there is not yet an official set of quality indicators, while this would be useful for benchmarking and to compare effect evaluations of interventions to improve the quality of diabetes care.

The delegation of tasks to nurses appears to improve process control, as process indicators improved and reached high levels when nurses were responsible for performing the annual check-ups. Concomitantly, outcome control appears to improve at the level of individually reached target values.

Ultimate proof of the effectiveness of these interventions can only be seen after analysing the development of complications as was done recently by Gaede *et al.*[41] The ZODIAC study has now entered its seventh year which will make the assessment of long-term effects of the presented interventions possible within the next few years.

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A patient with dyspnoea, subfebrile temperature and electrocardiographic abnormalities

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CASE REPORT

A 66-year-old man was admitted to our hospital because of dyspnoea and slightly elevated body temperature (38.1°C). A month before admission the patient suffered an ischaemic cerebrovascular accident. His medical history also revealed a myocardial infarction seven years ago and a transient ischaemic attack.

On physical examination his blood pressure was 130/80 mmHg, pulse 102 beats/min and regular; the central venous pressure was clearly elevated. The respiratory rate was 36 breaths/min. Examination of the lungs and heart revealed no abnormalities. The right lower extremity was red, warm and swollen and painful on palpation.

Laboratory tests were performed. An arterial blood sample showed no abnormalities. Lactate dehydrogenase was 566 U/l and troponin I 0.51 µg/l. A chest X-ray showed no abnormalities. His electrocardiogram (ECG) is shown in *figure 1*.

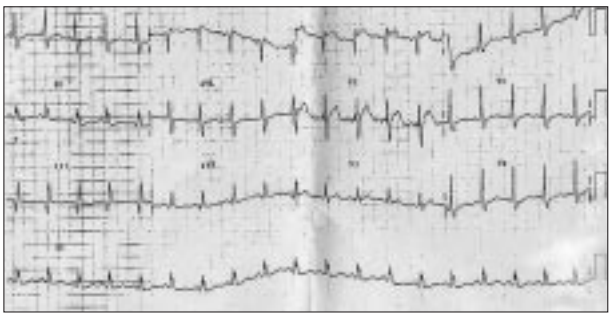

Figure 1
12-lead electrocardiogram of the patient

WHAT IS YOUR DIAGNOSIS?

See page 118 for the answer to this photo quiz.

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CASE REPORT

Tonsillar tuberculosis in a rheumatoid arthritis patient receiving anti-TNFα (adalimumab) treatment

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ABSTRACT

This case report describes a 61-year-old rheumatoid arthritis patient with an atypical clinical presentation of a sore throat. Because of rheumatoid arthritis refractory to conventional disease-modifying antirheumatic drug therapy, anti-TNFα was felt to be indicated, and a screening for tuberculosis was carried out. As the screening for tuberculosis (PPD) was positive, isoniazid was prescribed prophylactically for six months. After eight months of anti-TNFα (adalimumab) treatment, he developed tonsillar enlargement and nodular pulmonary lesions. Histopathological and microbial investigations established the diagnosis of tonsillar tuberculosis.

INTRODUCTION

Tumour necrosis factor α (TNFα) is a cytokine that plays an important role in the regulation of inflammatory processes. The proinflammatory cytokine TNFα, which is released by activated monocytes, macrophages and T lymphocytes, promotes inflammatory responses that are important in the pathogenesis of rheumatoid arthritis. Rheumatoid arthritis patients have high TNFα levels in the synovial fluid and subsequently develop bone erosion. Drugs blocking TNFα have been developed to neutralise these effects and to improve symptoms significantly.[1] One of these blocking agents is adalimumab (Humira), a recombinant human immunoglobulin G_1 monoclonal antibody.[2]

Inhibition of TNFα is associated with the risk of developing a serious infectious disease[3,4] as well as difficulty clearing infections once they have developed. One of the pathogens known to be capable of causing invasive disease in patients receiving TNFα blockade therapy is *Mycobacterium tuberculosis*.[5] TNFα in a soluble form increases the expression of adhesion molecules on endothelial cells and activates neutrophils and macrophages. Surface-bound TNFα is likely to be involved in cell-to-cell interactions, potentiating the activation of specific and nonspecific immune effector cells. The production of TNFα by alveolar macrophages has been shown to be essential in granuloma formation, chemokine production, leucocyte recruitment and the killing of intracellular pathogens, such as *Mycobacterium tuberculosis*.[6]

The purpose of this report is to point out that by applying modern anti-TNFα therapies we should increase awareness of potential complications such as tuberculosis, including extrapulmonary lesions, even when a patient follows the screening procedure and adheres strictly to a prophylactic treatment regimen for a period of six months.

CASE REPORT

A 61-year-old man visiting the rheumatology outpatient department for a routine check-up presented with a two-month history of sore throat, cough, fever, loss of appetite and weight loss of 10 kg. Two different antibiotics prescribed by his general practitioner did not relieve the symptoms. After 11 years of rheumatoid-factor-positive rheumatoid arthritis, he became refractory to treatment with sulphasalazine (2000 mg daily) and (parenteral) methotrexate (25 mg weekly). There was no history of prior infection, foreign travel or infectious contacts. He was married, worked as a construction labourer, smoked and consumed small

amounts of alcohol. For optimal suppression of the rheumatoid inflammation, a TNF-blocking agent was indicated. Prescreening for tuberculosis revealed a normal chest radiography but positive skin testing (10 tuberculosis units PPD) showing an induration of 4 x 4 cm. Bronchoalveolar lavage did not show active infection with tuberculosis. Ziehl-Neelsen staining and microbiological culture were negative. Despite these results prophylactic treatment with a regimen of isoniazid 300 mg daily for a period of six months was started. After five months of isoniazid, adalimumab 40 mg subcutaneously once every two weeks was started. His rheumatoid arthritis significantly improved: he was a good responder according to the DAS28 criteria.[7]
Seven months after the start of adalimumab and five months after the cessation of isoniazid the patient became ill. Chest radiography on a routine visit two months later showed nodular abnormalities (*figure 1*) and oral examination showed unilateral left tonsil enlargement. As malignancy was suspected a tonsil biopsy was performed. Histology revealed no malignancy but only vague granulomatous structures composed of central caseation necrosis with bacilli suspicious for mycobacteria. Polymerase chain reaction (PCR in-house)[8] gene probe demonstrated *Mycobacterium tuberculosis complex*. Sputum, bronchoalveolar lavage and tonsillar tissue were all negative for acid-fast bacilli by Ziehl-Neelson staining. Subsequently, cultures of these samples revealed *Mycobacterium tuberculosis* (INH susceptibility positive). Computed tomography confirmed lymphadenopathy in the neck region, mediastinum and upper abdomen. Tonsillar tuberculosis was diagnosed, probably secondary to pulmonary disease. The patient was placed on a regimen of isoniazid (300 mg daily), rifampicin (600 mg daily), ethambutol (400 mg daily) and pyrazinamide (500 mg daily). The patient was free of symptoms within three weeks. Adalimumab and methotrexate treatment were both stopped for the next six months. The tonsillar enlargement as well as the pulmonary lesions subsided. The rheumatoid arthritis remained in remission by applying sulphasalazine monotherapy.

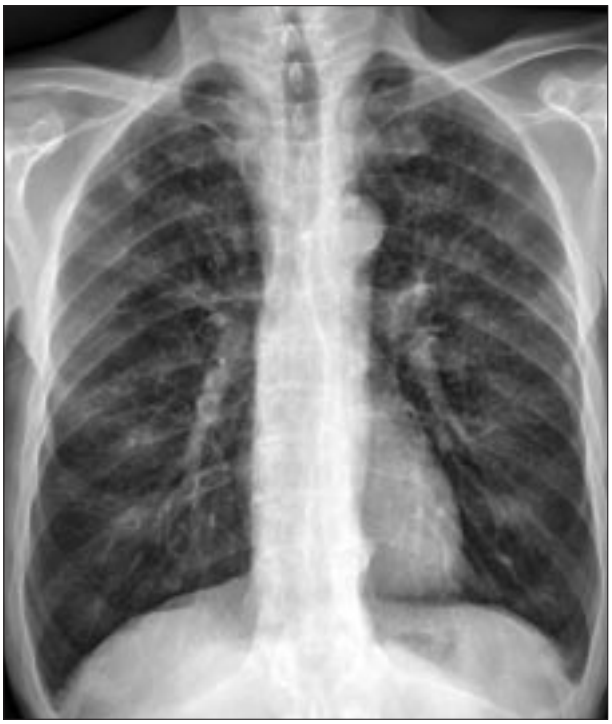

Figure 1
Chest X-ray showing nodular abnormalities, more pronounced in the upper than in the lower parts of the lungs

DISCUSSION

This case illustrates tonsillar tuberculosis as a sequel of anti-TNFα therapy. It is important to stress the atypical presentation of this severe opportunistic infection in anti-TNFα treated patients: the symptoms may mimic a conventional throat infection. Tuberculosis secondary to adalimumab has not yet been reported to the Netherlands Pharmacovigilance Centre (personal communication).
The diagnosis was made by identifying acid-fast bacilli in the tonsil biopsy material and confirmed by PCR. Tuberculosis observed after anti-TNFα therapy may be due to failure of compartmentalisation of viable *Mycobacterium tuberculosis* bacilli and therefore granulomas may not be seen. This patient may well have become ill due to an inadequate prophylaxis of six months for his latent tuberculosis. The extrapulmonary tuberculosis in this patient is probably secondary to primary pulmonary localisation although we have no data, i.e. microbiological, on the pulmonary abnormalities except for the nodular interstitial findings on chest radiography and computerised tomography. These interstitial findings subsided during and after treatment of the tuberculosis. In this patient the most likely period for acquiring the latent tuberculosis infection was the second world war.
Tuberculosis in patients receiving anti-TNFα therapy generally arises from the reactivation of latent infection and usually occurs within the first three to eight months of treatment. In a previous study of adalimumab therapy, tuberculosis developed in eight out of 542 patients.
The introduction of screening procedures and the use of lower doses of adalimumab reduced the frequency to five out of 1900 patients.[9]
The proportion of extrapulmonary and miliary cases, up to 40% of anti-TNFα therapy induced reactivation of tuberculosis, is similar for all TNFα antagonists.[10] Just prior to the era of TNFα blockade, oral manifestations of tuberculosis occurred sporadically and usually secondary to pulmonary disease.[10,11] So far one case of tuberculous

tonsillitis in a patient receiving etanercept has been reported.[12] Tuberculosis is not associated with the use of low-dose corticosteroids (i.e. prednisone at doses of 15 mg or less) and cytotoxic agents in rheumatic diseases.[13,14]
In June 2003 official Dutch guidelines for rheumatologists for prevention of tuberculosis in rheumatoid arthritis patients treated with anti-TNFα therapy were established.[15] The screening procedure includes, in addition to medical history and physical examination, intracutaneous testing and chest radiography. A subpopulation of immunocompromised patients may be anergic and may reveal a false-negative skin screening test.
If the screening reveals a latent infection, prophylactic treatment with isoniazid 300 mg daily for a period of at least nine months is now recommended. The effectiveness of isoniazid has been confirmed in randomised clinical trials and it can afford protection in up to 69 and 93% of those who strictly comply for six and nine months, respectively.[16,17] Prophylactic treatment should be given for at least three months before starting the TNFα blocking agent. The duration of isoniazid treatment turned out to be inadequate for the latent tuberculosis in the presented patient, immunocompromised by the treatment with immunomodulating drugs for his rheumatoid disease. An additional factor may be that the mycobacterium may have become resistant to isoniazid.

Studies indicate that other chronic inflammatory diseases, for example severe psoriasis, will benefit from anticytokine therapy as well. An increasing number of specialists will probably treat patients in the near future with anti-TNFα for an increasing number of indications. Given the highly effective reduction in disease activity achieved by these agents some adverse outcome should probably be accepted. However, patient and physicians must be aware that during anti-TNFα therapy the course of infections may be fulminant and life threatening. In addition, clinical and laboratory signs may be blunted by TNFα blockade and by concomitant immunosuppressive medication. Therefore, only specialists familiar with the indications as well as the increased risks of tuberculosis and other opportunistic infections should prescribe these potent agents. Careful evaluation at the initiation of the treatment as well as long-term surveillance of the patients receiving such drugs remains necessary: patient selection, education and safety monitoring should maximise patient safety.

ACKNOWLEDGEMENTS

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Isolated perianal tuberculosis

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ABSTRACT

Perianal tuberculosis, without the presence of any previous or active pulmonary infection, is extremely rare. A case of isolated perianal tuberculosis without gastrointestinal or pulmonary spread will be discussed here with an evaluation of the clinical features.

INTRODUCTION

The incidence of pulmonary tuberculosis has decreased and extrapulmonary tuberculosis has become very rare with the introduction of effective antituberculous chemotherapy. However, although the rates of mortality and morbidity due to tuberculosis are decreasing, it has been reported that there is an increase in the cases of tuberculosis due to the increasing incidence of acquired immune deficiency syndrome (AIDS).[1] On the other hand, perianal tuberculosis, without the presence of previous or active pulmonary infection, is extremely rare. Here, we present a case of isolated perianal tuberculosis without gastrointestinal or pulmonary spread.

CASE REPORT

An 80-year-old male patient was admitted with a history of perianal discharge and ulceration for the last six months. Treatment with topical antibiotics and epithelialising ointment had been ineffective. The patient was afebrile on admission. No lymphadenopathy was found on palpation, and physical examination of the respiratory tract was normal. No palpable mass or organomegaly was detected on abdominal examination.

There was an ulceration in the left perianal region with a transverse diameter of 4 cm and vertical diameter of 3 cm (*figure 1*). Digital rectal examination revealed no pathological findings. Anoscopy was normal and no fistulas were noted. Laboratory studies showed normal values of haemoglobin, haematocrit, total leucocyte count, platelets and erythrocyte sedimentation rate. Liver enzymes and renal function tests were also within the normal range. Chest X-ray revealed no pathological findings.

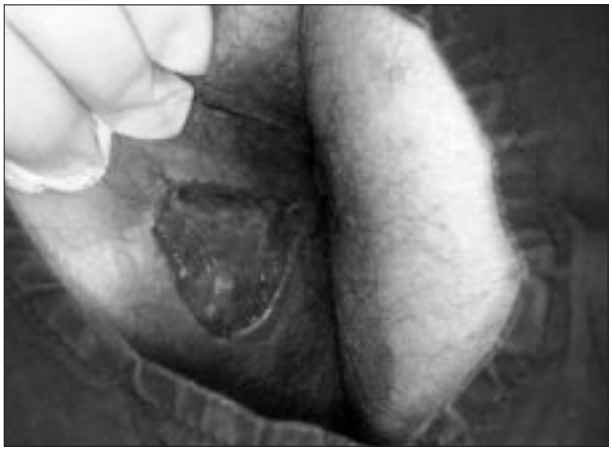

Figure 1
An ulceration in the left perianal region at line 7 by proctological position, starting 2 cm from the anus, with a transverse diameter of 4 cm and vertical diameter of 3 cm was observed on admission

The perianal lesion was curetted and biopsy material was taken. Since only nonspecific granulation was found in the first biopsy, a second biopsy was performed a week later. Histological examination of the second biopsy showed epithelioid granulomas, Langhans' type multinucleated giant cells, caseous necrosis, and acid-fast bacilli. In addition, polymerase chain reaction (PCR) was positive for mycobacterium tuberculosis. A PPD test revealed a negative reaction with 4 mm of induration. PCR assays of the sputum collected on three subsequent days were negative for tubercle bacilli. Double-contrast barium studies of colon and small bowel were normal. No pathological findings were detected on upper gastrointestinal endoscopy and rectosigmoidoscopy. Computed tomography of the abdominal and pelvic region revealed no pathological findings either. Human immunodeficiency virus antibody test was negative.

We made a diagnosis of isolated perianal tuberculosis and started triple antituberculous treatment consisting of isoniazid (300 mg/day), rifampicin (600 mg/day), and pyrazinamide (2 g/day) No side effects occurred. His symptoms resolved and the perianal ulcer began to heal within the first month of treatment (*figure 2*). From the culture of the biopsy specimen, tubercle bacilli were isolated on Lowenstein-Jensen medium in the eighth week of

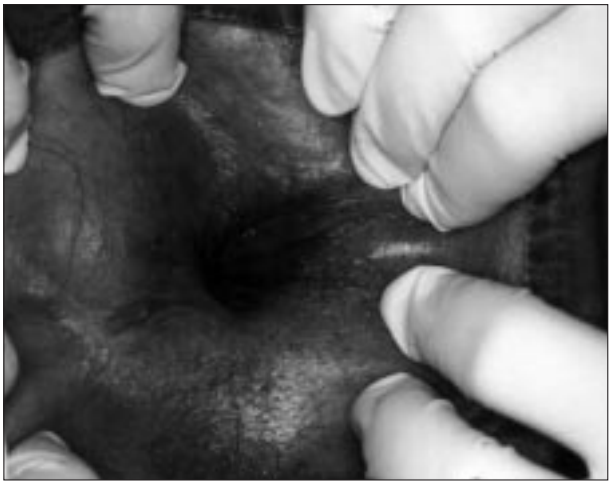

Figure 2
Healing of the ulcer within the first month of antituberculous treatment

treatment. Therapy with isoniazid and rifampicin was continued for six months. After six months, the lesion had disappeared, and only a mild granular region remained (*figure 3*). The patient is healthy without any symptoms and there is still no recurrence after one year of follow-up.

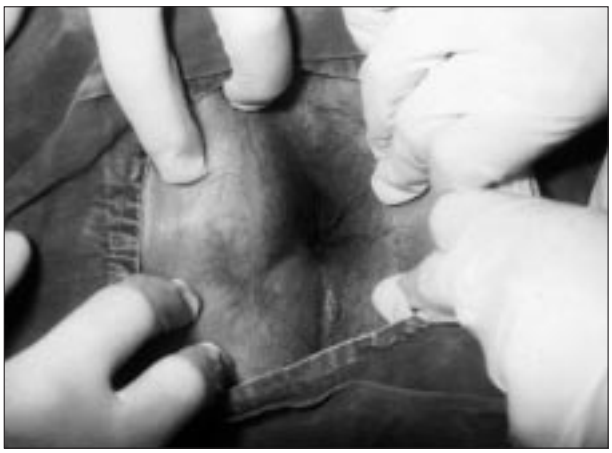

Figure 3
Recovery of the lesion (only a mild granular region was observed at the same localisation at the sixth month of the treatment)

DISCUSSION

We present here a case of perianal tuberculosis in an elderly patient without HIV infection. The incidence of tuberculosis of the gastrointestinal tract has dramatically decreased in the last few decades. Development of antituberculosis chemotherapies and widespread use of pasteurised milk have played a major role in this decrease. In addition, better recognition of Crohn's disease prevents it from being misdiagnosed as gastrointestinal tuberculosis. However, tuberculosis of the gastrointestinal tract is still present in developing countries, particularly in large migratory communities. Recently, the number of cases of tuberculosis has shown a tendency to increase with the rising number of cases with AIDS in developed countries.[1] Extrapulmonary tuberculosis is responsible for 15% of all cases of tuberculosis. Extrapulmonary spread mainly consists of involvement of the pleura (26%), lymph nodes (17%), genitourinary tract (15%), bones and joints (14%), meninges (6%), peritoneum (4%) and miliary TB (8%).[2,3] Tuberculosis of the gastrointestinal tract is responsible for 1% of all cases of tuberculosis. Tuberculosis may involve any part of the gastrointestinal system, such as the peritoneum, stomach, duodenum, ileocaecal region, colon, rectum, and anus. Of these, tuberculous peritonitis is the most common.[2] The most frequently affected part of intestinal tract is the ileocaecal region. Involvement of the appendix and jejunum is uncommon, and spread to the anus is much rarer.[4] Tuberculosis of the gastrointestinal tract usually occurs as a result of spread from tuberculosis foci in the lungs. Ingestion of the bacilli from sputum may lead to invasion of the intestinal wall. Harland *et al.* presented two cases diagnosed as anal tuberculosis

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associated with pulmonary tuberculosis.[5] Sultan *et al.* documented data of seven cases of anoperineal tuberculosis observed between 1982 and 1999, and an association with pulmonary tuberculosis was found in each case.[6] However, pulmonary tuberculosis may not be present and intestinal and peritoneal disease may develop by reactivation of the latent focus. Other mechanisms that have been considered are haematogenous spread and retrograde spread of *M. tuberculosis* into abdominal lymph nodes from a pulmonary site.[7] In our patient, no pulmonary or gastrointestinal focus was found despite an extensive investigation.

Perianal tuberculosis may manifest as an ulcerative, verrucous, lupoid and miliary form. The most common type is the ulcerative lesion which tends to have well-defined boundaries and be characterised by mucopurulent discharge. The verrucous type tends to extend into the anal passage from the perianal region with a development pattern similar to that of a wart. However, it may appear as a haemorrhoidal nodule, perianal abscess or anal fistula.[7,8] Our patient presented with perianal ulceration, and no abscess or anal fistula was noted.

Crohn's disease plays a significant role in the differential diagnosis of perianal tuberculosis, and other conditions that should be considered are ulcerative colitis, herpes simplex lesions, syphilis, sarcoidosis, amebiasis, deep mycosis, lymphogranuloma venereum, and ulcerative neoplasms.[7,9] Differentiating between perianal tuberculosis and Crohn's disease may be difficult. Both conditions have certain similar features including colonic skip lesions, ileocaecal spread and granulomas on histological examination. These two diseases may be difficult to distinguish from each other by macroscopic evaluation, and microscopic examination is needed. When tuberculosis is considered, a biopsy needs to be taken from the lesion; acid fast staining and if available polymerase chain reaction should be used for a rapid and accurate diagnosis. Finally cultures are needed to confirm the diagnosis and susceptibility testing.

CONCLUSION

In conclusion, since it is an extremely rare aetiological cause in patients with anal discharge and ulceration, the diagnosis of perianal tuberculosis is difficult to make when there is no pulmonary focus. It has to be kept in mind that cases of perianal tuberculosis may appear as incipient disease without the presence of any previous or active pulmonary infection. Tuberculosis has to be considered in the differential diagnosis of perianal ulcers since treatment with antituberculous agents may provide complete recovery.

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ANSWER TO PHOTO QUIZ (ON PAGE 111)

A PATIENT WITH DYSPNOEA, SUBFEBRILE TEMPERATURE AND ELECTROCARDIOGRAPHIC ABNORMALITIES

DIAGNOSIS

The ECG showed a sinus tachycardia of 111 beats/min, an incomplete right bundle branch block and a so-called McGinn-White S1Q3T3 pattern.[1] There were no signs of acute ischaemia.
Because a pulmonary embolism was considered, a high-resolution spiral computed tomography angiography was performed.[2] This showed a massive pulmonary embolism presenting as a classic saddle embolus at the bifurcation of the main pulmonary artery extending into the left and right pulmonary arteries (*figure 2*).

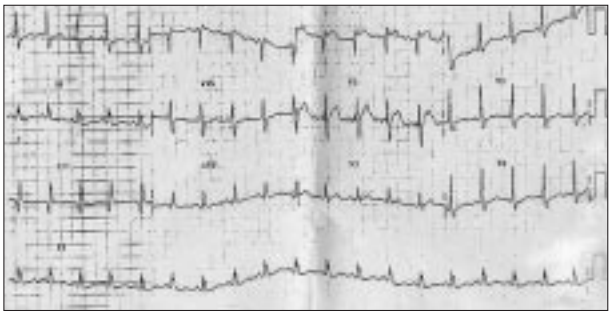

Figure 2
High-resolution spiral CT-scan angiography presenting the saddle embolus

A transthoracic echocardiography was performed which showed dilatation of the right ventricle with tricuspid regurgitation and systolic pulmonary artery hypertension of 58 mmHg, compatible with massive pulmonary embolism.[3]
The patient was treated with intravenous heparin/low-molecular-weight heparin and acenocoumarol. Because of a recent cerebrovascular accident we considered thrombolytic therapy to be contraindicated.[4,5] After eight days the patient was discharged. During follow-up the patient remained asymptomatic.

Classic features of massive pulmonary embolism at electrocardiography[1] and echocardiography[3]:
- Sinus tachycardia
- (Incomplete) right bundle branch block
- McGinn-White S1Q3T3 pattern, which means S wave in lead I, Q wave in lead III and a flattened or negative T wave in lead III
- Right ventricular dilatation and systolic pulmonary hypertension

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Bijsluiters

Bijsluiters

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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.

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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.

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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.

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1. Smilde TJ, van Wissen S, Wollersheim H, Kastelein JJP, Stalenhoef AFH. Genetic and metabolic factors predicting risk of cardiovascular disease in familial hypercholesterolemia. Neth J Med 2001;59:184-95.
2. Kaplan NM. Clinical Hypertension. 7th ed. Baltimore: Williams & Wilkins; 1998.
3. Powell LW, Isselbacher KJ. Hemochromatosis. In: Braunwald E, Fauci AS, Kasper DL, et al., editors. Harrison's Principles of Internal Medicine. 15th edition. New York: McGraw-Hill; 2001. p. 2257-61.

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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.

Case reports

Case 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.

Letters to the editor

Letters to the editor referring to articles previously published in the journal will be considered by the editors; letters should be no more than 500 words and sent both on disk or e-mail and in hard copy.

Books for reviewing

Books, which are to be considered for review, should be sent to the Editor in chief.

Submission

Manuscripts should be sent to the Editor in chief, Prof. A.F.H. Stalenhoef, Radboud University Nijmegen Medical Centre, Department of General Internal Medicine (541), 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.

Reviewing process

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.

Proofs

Proofs will be sent to the authors to be carefully checked for printer's errors. Changes or additions to the edited manuscript cannot be allowed at this stage. Corrected proofs should be returned to the editorial office within two days of receipt.

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These are not available. The first author receives two sample copies of the journal with the published article.