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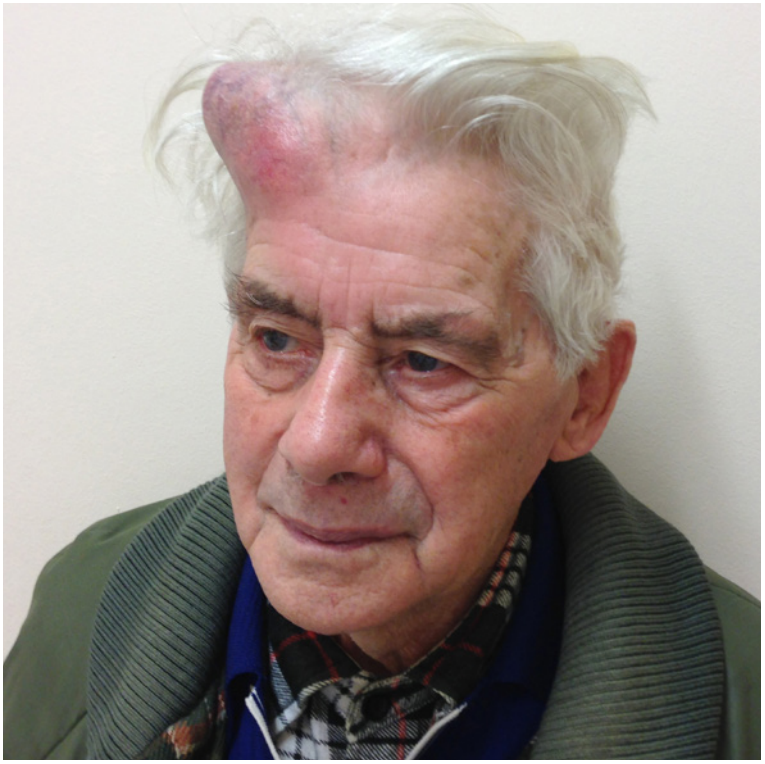

A man with a swelling on his scalp; what is your diagnosis?

Diabetes in patients with HIV

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Adherence to guidelines to prevent cardiovascular disease

•

Factors influencing completion times in an emergency department

•

Clozapine intoxication

August 2015, VOL. 73, NO. 7, ISSN 0300-2977

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EDITORIAL

Cardiovascular disease prevention: Mind the gap...

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Cardiovascular disease (CVD) is still one of the leading causes of reduced quality of life, disability and death. This is unfortunate, as we know that much of CVD morbidity and mortality can be avoided by application of primary and secondary prevention measures. Evidence-based guidelines for prevention of CVD have been developed worldwide. However, to accomplish their envisioned effect, adherence to the guidelines is of utmost importance.

Lifestyle, smoking, dyslipidaemia, hypertension and hyperglycaemia are modifiable risk factors for CVD. In the past decades, significant improvement has been made in the treatment and prevention of CVD, already leading to more favourable health outcomes.[1,2] Nonetheless, past surveys in several countries, including the Netherlands, have shown that CVD prevention guidelines are incompletely applied.[3-7] The lack of implementation of proven effective strategies is an 'evidence-practice gap'.[8] More specifically, this is an 'under-use evidence-practice gap'. An 'under-use evidence-practice gap' leads to much smaller health benefits compared with what could potentially be achieved if the guideline was optimally deployed.

In this issue of the Netherlands Journal of Medicine, Balder *et al.* describe a clear 'under-use evidence-practice gap' in the Netherlands.[9] They investigated the reported use of lipid-lowering drugs as a proxy of the adherence to the Dutch National guidelines for prevention and treatment of CVD. They find astonishingly low numbers of people eligible for treatment that are actually using lipid-lowering drugs (23% for primary prevention and 69% for secondary prevention). Looking further at the data, people being treated have an average LDL-cholesterol level of 2.6 mmol/l and 2.4 mmol/l for primary and secondary prevention, respectively. This means that part of the treated group will not have reached the treatment goal of LDL-cholesterol <2.6 mmol/l, which makes the results even more disappointing with regards to guideline adherence.

It has been extensively shown that LDL-cholesterol lowering by only 1 mmol/l reduces major vascular events by about 20%, major coronary events by about 25%, coronary revascularisations by about 25%, and ischaemic stroke by just under 20%, These findings apply to both men and women and to both primary and secondary prevention.[10,11] Moreover, lipid-lowering interventions are cost-effective and may improve quality of life, with low rates of adverse events. Considering these numbers, there should be no doubt that lipid lowering is useful. And this leads us to the question why guideline adherence is as poor as it is. Balder *et al.* identify some risk factors for not being treated according to the guideline, for example female gender in secondary prevention. Still, these risk factors do not fully clarify why the guideline is not adequately implemented. Are caretakers not adhering because of unawareness of their risk and risk factors? Do they experience side effects or other objections to the therapy? Are caregivers not adhering by not (correctly) assessing the risk in their patients? Are they not prescribing medication when indicated, and if so, why not? Or is our healthcare system not designed in a way that allows the guidelines to be implemented in the most effective way? These and many other questions should be answered to come up with strategies to improve the percentage of patients receiving the treatment they deserve.

Taken together, even though we do not know the exact reasons for non-adherence to the guidelines, the study by Balder *et al.* gives us a strong indication that a large number of people in the Netherlands are not receiving primary and secondary prevention measures for lipid lowering, while they should. Gaining a better understanding of the underlying causes and motivations for non-adherence to the guidelines is critical for designing effective interventions to improve public and physician awareness and adherence.

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ORIGINAL ARTICLE

Diabetes in patients with HIV: patient characteristics, management and screening

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ABSTRACT

Background: As HIV management has become more successful during the past years, non-communicable diseases have become more prevalent among HIV-infected individuals. As a result, more HIV-infected patients die of cardiovascular diseases, with diabetes being one of the main risk factors. This study evaluates screening and management of diabetes among HIV-infected patients in a university hospital in the Netherlands.

Methods: We examined clinical characteristics, glycaemic control and cardiovascular risk management of HIV-infected patients with coexisting diabetes, and determined the frequency of diabetes screening in those without.

Results: Of 518 HIV-infected patients, 28 had been diagnosed with diabetes (5.4%), mostly (20/28) after being diagnosed with HIV. Patients with coexisting diabetes were older, had a longer duration of HIV, lower CD4 cell counts and higher body mass index (BMI), and were more likely to use aspirin, statins and antihypertensive medication than those without diabetes (all $p < 0.05$). HbA1c values were below 7% (53 mmol/mol) in 54% of patients. Targets for systolic blood pressure (< 140 mmHg), LDL cholesterol (< 2.5 mmol/l) and BMI (< 25 kg/m^2) were achieved by 82%, 50% and 29% of patients, respectively. Annual ophthalmology examination, screening for microalbuminuria and foot control were rarely performed. Among the patients without known diabetes, diabetes screening during the past year had been performed using (non-fasting) plasma glucose in 56% and HbA1c in 10%, but 42% of patients had not been screened.

Conclusion: For HIV-infected individuals with diabetes, glycaemic control and cardiovascular risk management were reasonable, but screening for microvascular complications was rarely performed. Annual diabetes screening of HIV-infected patients was not routine.

KEYWORDS

Cardiovascular risk factor management, diabetes, HIV, quality of care, screening

INTRODUCTION

The widespread use of combined antiretroviral therapy (cART) has significantly reduced the risk of infectious complications and improved overall survival in patients infected with human immunodeficiency virus (HIV). With the increased success of the treatment of HIV infection, diabetes and other chronic non-communicable diseases (e.g. hypertension and dyslipidaemia) and their complications have become more prevalent.[1] As a consequence, a substantial proportion of HIV-infected patients die from vascular events rather than from opportunistic infections or other AIDS-defining illnesses.[2] Greater emphasis on the management of the traditional risk factors for cardiovascular diseases is especially important in patients with coexisting diabetes mellitus, because this condition is in itself a cardiovascular risk equivalent.

The prevalence of diabetes has been estimated at 3-14% among HIV-infected individuals and is growing.[3-8] Most of these patients develop diabetes after being diagnosed with HIV infection. Insulin resistance plays a prominent role in the development of diabetes in HIV-infected individuals, even at normal body weight.[9] A major contributor to insulin resistance is treatment with cART, partly through a direct effect on insulin-mediated glucose transport and in part through the occurrence of dyslipidaemia and lipodystrophy.[10] Besides increasing age, other factors that are associated with diabetes in HIV-infected patients include low CD4 count and coexistent hepatitis C infection next to general risk factors for the development of diabetes

(e.g. high triglycerides).[11,12] The European AIDS Clinical Society therefore recommends measuring fasting plasma glucose at HIV diagnosis, before initiating cART, and at least annually thereafter.[13]

Currently, there are no specific guidelines for the management of diabetes in patients with HIV, except for references to general diabetes treatment recommendations and the instruction to screen HIV patients for diabetes.[13,14] It is unclear to what extent these general guidelines for diabetes are being implemented in HIV care. Indeed, HIV-infected patients are often treated by infectious disease specialists who are less experienced in endocrinology or diabetology, and who may be more focused on managing HIV per se rather than the metabolic sequelae, although this may be different in general teaching compared with university hospitals. To address some of these issues, we describe the characteristics and current management of patients with HIV and diabetes in a cohort of HIV-infected patients in a university hospital in the Netherlands.

MATERIALS AND METHODS

We conducted a retrospective survey among patients with HIV who visited the outpatient clinic of the Radboud university medical centre between August 2012 and November 2013. All of the 518 HIV-positive patients were included. Patients with diabetes mellitus were identified from the clinic's database, in which diabetes diagnosis was based on documentation by their specialist or use of glucose-lowering agents. The distinction between type 1 and type 2 diabetes was made on clinical grounds, anti-GAD antibodies were only measured sporadically. The following information was collected from all subjects using the database and individual case records: gender, age, race, weight, height, smoking status, age at HIV diagnosis, CD4 cell count, viral load, type of cART, glucose, HbA1c, mean blood pressure, last measured lipid values, serum creatinine and use of other medication. For all patients with diabetes, additional data were collected including type of diabetes, age at diabetes diagnosis, use of insulin or other glucose-lowering medication, and urinary albumen excretion (by albumen-to-creatinine ratio, if available). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

According to the national general practitioners guideline for managing diabetes (Dutch NHG standard),[15] goals for diabetes care were defined as: HbA1c < 7% (53 mmol/mol), fasting plasma glucose < 7 mmol/l, systolic blood pressure < 140 mmHg, LDL cholesterol < 2.5 mmol/l, triglycerides < 4.5 mmol/l and BMI < 25 kg/m^2. Besides achievement of treatment goals, we evaluated the frequency of monitoring relevant parameters including body weight, blood pressure, examination of lower extremities for neuropathy and peripheral artery disease, fasting glucose, HbA1c, serum creatinine and lipids, albumen-to-creatinine ratio in spot urine samples, and ophthalmology examinations in all patients with diabetes.

Statistical analysis was conducted using SPSS, version 19. Categorical variables were compared using Pearson's chi-square. Continuous variables were compared using Student's t test when normally distributed; the Mann-Whitney U test was used when variables were not normally distributed. Results were considered statistically significant if the corresponding P-value was < 0.05.

RESULTS

Of 518 HIV-infected patients, 28 (5.4%) had diabetes, mostly type 2 (n = 25, 89%). Twenty patients were receiving cART before diabetes was diagnosed (71%), while in eight patients diabetes was diagnosed before HIV. Diabetes was treated with insulin in 36%, either alone or in addition to oral medication, and with oral glucose-lowering drugs only, mostly metformin, in 60%. Antihypertensive drugs, lipid-lowering agents and platelet inhibitors were used by 68%, 57% and 25% of diabetic patients, respectively (*table 1*).

Apart from higher glucose and HbA1c levels, patients with HIV and concurrent diabetes were older, were more likely to be overweight, and had higher triglyceride levels compared with patients without diabetes. There were no differences in blood pressure, whereas total and LDL cholesterol levels were even lower in patients with diabetes, probably due to more frequent use of blood pressure and cholesterol-lowering medication (*table 1*). With respect to HIV status, HIV-infected patients with diabetes were more likely to have a CD4 cell count < 200 cells/µl, despite a longer duration of HIV treatment (OR 5.6, p = 0.02). More patients with diabetes used integrase inhibitors; physicians probably opted for this relatively new class of cART because they are less toxic compared with the older drugs, metabolically neutral and only rarely cause drug interactions.

Figure 1 displays the proportion of patients with HIV and diabetes achieving treatment goals, as recommended by Dutch General Practitioner's guidelines on cardiovascular risk management in people with diabetes.[15] Systolic blood pressure was below the target of 140 mmHg among 23 patients (82%), but fewer patients reached the other treatment targets (29-64%). None of the patients met all the treatment targets, while five patients (18%) had only one treatment goal on target.

The quality of diabetes management was assessed by measuring various process indicators on biomarkers for cardiovascular risk and screening for microvascular

Table 1. *Demographic and disease related characteristics of HIV-infected patients with or without diabetes*

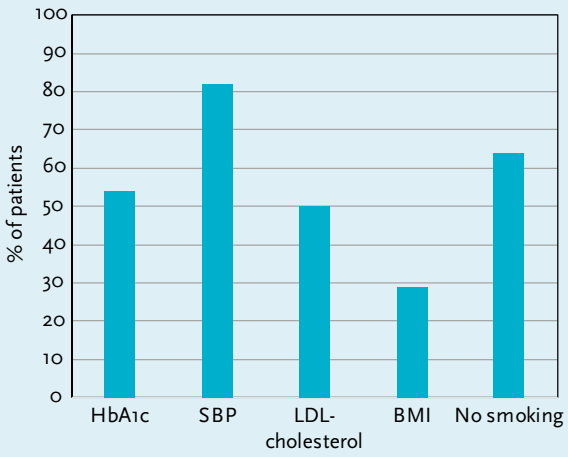
Variable	HIV alone (n = 490)	HIV and diabetes (n = 28)	P-value
Demographics			
Male sex (%)	397 (81)	22 (79)	0.92
Age (years)	46±11	53±11	0.001
Race/ethnicity (%)			
European	382 (78)	21 (75)	0.70
African	65 (13)	5 (18)	0.49
Other	42 (9)	2 (7)	0.80
Body mass index (kg/m²)	24±4	27±4	
<25	270 (55)	6 (21)	<0.001
25-30	173 (35)	17 (61)	<0.001
>30	26 (5)	4 (14)	0.05
Lipid values (mmol/l):			
Total cholesterol	4.8 (4.2-5.5)	4.3 (3.6-4.7)	0.003
LDL cholesterol	2.9±0.88*	2.6±0.95	0.043
Triglycerides	1.4 (1.0-2.0)	2.4 (1.4-3.5)	<0.001
Blood pressure (mmHg)			
Systolic blood pressure	126±15	133±16	0.98
Diastolic blood pressure	78±11	81±8	0.17
Diabetes related			
Age at diabetes diagnosis (years)	NA	44±9	
Diabetes duration (years)	NA	9±5	
HbA1c (mmol/mol)	ND	51 (44-65)	
Diabetes medication (%):	NA	27 (96)	
Insulin		10 (36)	
Metformin		20 (71)	
Sulfonylurea		11 (39)	
DPP-4 inhibitor		1 (4)	
Renal function			
Serum creatinine (mmol/l)	78 (68-80)	78 (60-90)	0.423
Albumin-creatinine ratio (mg/mmol)	ND	3.2 (0.9-5.5)‡	
HIV related			
Age at HIV diagnosis (years)	37±11	41±10	0.034
HIV duration (years)	8±6	12±7	0.007
CD4 cell count (cells/µl)	580 (440-750)	540 (340-740)	0.310
CD4 cell count (cells/µl) <200	17 (3)	4 (14)	0.004
Negative HIV-RNA (%)	383 (78)	24 (86)	0.20
ART (%)			
NRTI	439 (90)	25 (89)	0.96
NNRTI	255 (52)	15 (54)	0.88
PI	134 (27)	6 (21)	0.49
II	88 (18)	9 (32)	0.06
Cardiovascular medication (%)			
Antihypertensive drugs	62 (13)	19 (68)	<0.001
Lipid-lowering drugs	89 (18)	16 (57)	<0.001
Aspirin	29 (6)	7 (25)	<0.001

Data were available for > 90% of patients, unless stated otherwise, and are shown as number (%), as mean ± standard deviation or as median and interquartile range (IQR) *data missing in 14% of patients, ‡data missing in 50% of patients. DPP-4 inhibitor = dipeptidylpeptidase-4 inhibitor; ART = antiretroviral therapy; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor, II = integrase inhibitor; NA = not applicable; ND = no data.

complications (*figure 2*). Plasma glucose levels or HbA1c were measured at least once a year in all patients. Body weight, blood pressure and lipids were measured at least once a year in 75%, 86% and 71% of patients, respectively. Renal function was determined once a year in all patients, but screening for urinary albumen excretion was missing in 71% of the patients. Information on foot and eye examinations was lacking in 89% and 75% of patients, respectively. Two-yearly eye examination was performed in 36% of patients.

Finally, we evaluated how often the HIV population without diabetes was screened for the presence of diabetes.

Figure 1. *Proportion of patients achieving target values for cardiovascular risk factors as recommended by the Dutch diabetes guideline*



Recommended targets: HbA1c < 7%/53 mmol/mol, systolic blood pressure < 140 mmHg, LDL cholesterol < 2.5 mmol/l, BMI < 25 kg/m².

Plasma glucose concentrations, fasting or non-fasting, had been measured in 56% of these patients during the past year and at least once in 99% of patients in the past 12 years. Similarly, measurement of HbA1c was performed in 10% and 32% of patients during the past year and in the past 12 years, respectively. During the past year, 42% of HIV-infected patients without diabetes had no plasma glucose or HbA1c measured.

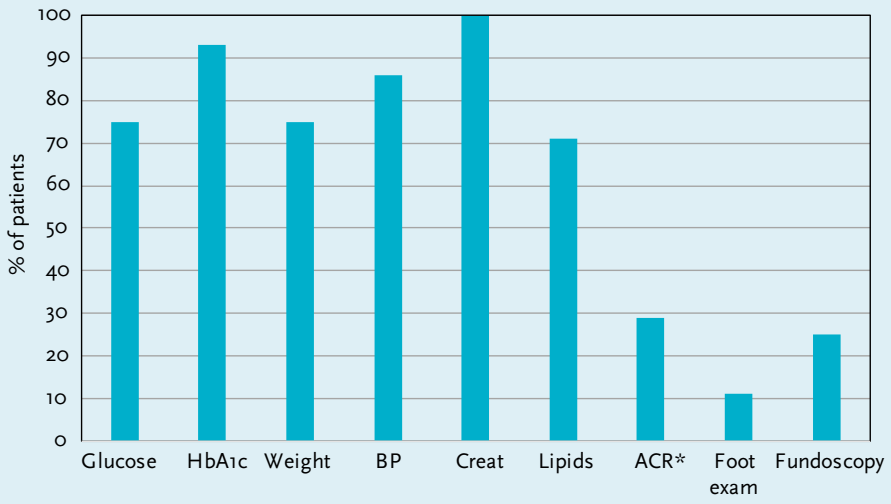
DISCUSSION

In this single-centre cohort of HIV-infected patients, we found a prevalence of diabetes of 5.4%, which is in line with previously reported estimates of diabetes prevalence among HIV-infected patients.[3-7] The majority of patients had developed diabetes after having been diagnosed with HIV, and all of these patients were on cART at the time of diabetes diagnosis. HIV duration was longer and CD4 cell counts were slightly lower in patients with concurrent diabetes than in those without diabetes. Diabetes and cardiovascular risk factor control was reasonable and not much different from what is reported for the diabetes population as a whole.[16] However, HIV-infected patients with diabetes were rarely screened for microvascular complications.

To our knowledge, this is the first study examining differences in phenotype between HIV-infected patients with and without diabetes mellitus. We found that patients with diabetes were significantly older and more often overweight compared with HIV-infected patients without diabetes. There appeared to be sufficient awareness for other cardiovascular risk factors in patients with concurrent diabetes, as reflected by the majority of patients achieving the blood pressure target and the high proportion of patients using blood pressure and lipid-lowering drugs.

There were few differences in HIV-related parameters between patients with and without coexisting diabetes. The slightly greater proportion of patients with diabetes with a CD4 count < 200 cells/µl may suggest an adverse effect of diabetes on immunological response to cART,

Figure 2. *Proportion of patients receiving yearly screening of most important treatment goals, as recommended by the Dutch diabetes guideline*



BP = blood pressure; Creat = creatinine; ACR = albumen-to-creatinine ratio.

independent of age and duration of HIV infection. This has to be interpreted carefully as this is only based on four patients. Nevertheless, low CD4 counts in HIV-infected patients have previously been associated with increased risk of non-communicable diseases, such as diabetes.[17]

About 50% of our patients achieved the glycaemic target set at an HbA1c of < 53 mmol/mol, which is in line with previous reports.[18,19] It should be noted, however, that subclinical haemolysis induced by antiretroviral therapy may interfere with HbA1c measurement,[20] causing a slight overestimation of the proportion of patients reaching the glycaemic target.

Our findings regarding achieving other diabetes-related treatment goals corroborate in a large part with those of Adeyemi *et al.*, who examined to what extent goals recommended by the American Diabetes Association (ADA) were met in 216 HIV-infected patients with diabetes.[19] The only exception was that less of their patients achieved the ADA blood pressure target. However, since the average blood pressure values were comparable with our data, the latter was probably related to the stricter blood pressure target used (< 130/80 mmHg versus < 140 mmHg).

Most diabetes guidelines recommend at least annual testing of HbA1c (or fasting plasma glucose), serum creatinine, lipids, blood pressure and body weight, as well as screening for retinopathy, nephropathy and neuropathy.[21] Management of our patients with coexisting HIV was largely in line with these recommendations, except that screening for microvascular complications was insufficiently performed.

Because of the high risk of diabetes in HIV-infected patients, the European Aids Clinical Society recommends screening all patients for elevated glucose levels at HIV diagnosis, before starting therapy and yearly thereafter.[13] In this study, almost the entire population had been screened for diabetes at some point from the moment they entered the database. However, screening was not performed in the past year in 42% of patients, which means that the actual prevalence of diabetes in our population may in fact be higher. Early diagnosis of diabetes is important to allow timely initiation of modifiable cardiovascular risk-reducing strategies. Indeed, the risk of myocardial infarction in patients with HIV and diabetes has been shown to be more than twice as high as in healthy subjects.[22]

This study has several limitations. Because it is a relatively small study from a single university hospital, our results cannot be simply generalised to the entire HIV population. Second, we cannot exclude that some examinations were performed by the general practitioner, although from reviewing individual patient records this only appears to happen rarely, as many HIV-infected patients discuss most health-related issues, including diabetes, with the HIV management team.

This study clearly shows there is room to improve the management of diabetes among HIV-infected patients. Routine screening for diabetes in the non-diabetic HIV population was suboptimal and our analysis disclosed a blind spot with respect to microvascular complications in HIV-infected patients with coexistent diabetes. Future studies should focus on the best and most cost-effective way of delivering appropriate diabetes care to HIV-infected patients. More awareness is needed, as diabetes prevalence will probably increase in the future, especially in the light of an ageing population of HIV-infected patients.

DISCLOSURES

The results presented in this paper have not been published previously in whole or part, except in abstract form at the national Annual Dutch Diabetes Research Meeting 2013 in Oosterbeek, the Netherlands.

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ORIGINAL ARTICLE

Adherence to guidelines to prevent cardiovascular diseases: The LifeLines cohort study

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ABSTRACT

Background: Cardiovascular disease (CVD) is the leading cause of death worldwide. While there is indisputable evidence that statin treatment reduces the burden of CVD, undertreatment remains a concern for primary and secondary prevention. The aim of this study was to assess the use of lipid-lowering drugs (LLD) among 70,292 individuals in the Netherlands as a proxy of adherence to the national guideline for prevention and treatment of CVD.

Methods: LifeLines is a population-based prospective cohort study in the three Northern provinces of the Netherlands. At baseline, all participants completed questionnaires, and underwent a physical examination and lab testing. The national guidelines were used to assess how many participants were eligible for LLD prescription and we analysed how many indeed reported LLD use.

Results: For primary prevention, 77% (2515 of 3268) of those eligible for LLD treatment did not report using these drugs, while for secondary prevention this was 31% (403 of 1302). Patients with diabetes mellitus were treated best (67%) for primary prevention. Notably, of the patients with stroke, only 47% (182 of 386) reported LLD treatment.

Conclusion: Despite clear guidelines and multiple national initiatives to improve CVD risk management, adherence to guidelines for the treatment of CVD in the Netherlands remains a major challenge. This study calls out for improving public awareness of CVD and to improve primary and secondary prevention to prevent unnecessary CVD-related morbidity and mortality.

KEYWORDS

Cardiovascular risk, primary prevention, secondary prevention, statins, undertreatment, underuse, risk assessment

INTRODUCTION

In the early 1990s, several landmark trials unequivocally showed that HMG-CoA reductase inhibitors, i.e. statins, reduce cardiovascular morbidity and mortality in secondary as well as primary prevention through lowering low-density lipoprotein cholesterol (LDL-c) levels.[1,2]

There are to date only very few reports on the use of statins for primary prevention. Data from the Oslo Health Study (collected in 2000-2001) showed that most participants with diabetes were not treated, especially women.[3] In 2003, it was shown that over 95% of the population eligible for pharmacological treatment of hypercholesterolaemia were untreated or uncontrolled in a Dutch population-based cohort study.[4] It was subsequently shown that the use of cardiovascular drugs increased over time in the Netherlands,[5] but recent figures on the implementation of cardiovascular disease (CVD) guidelines for the use of lipid-lowering drugs (LLD) for primary and secondary prevention are lacking. The need for continuous awareness was recently illustrated by the observation in the USA that only 20% of individuals with a ten-year CVD risk > 20% were treated with statins.[6]

For patients who suffered from CVD (secondary prevention), several studies in the late 1990s highlighted

that undertreatment was also common.[7] In a representative survey of the US population, it was recently shown that only 58% of patients with coronary artery disease were treated with statins.[8]

The general aim of guidelines is to assist physicians in selecting the best treatment strategy for an individual patient. The indication to prescribe LLD in the Netherlands is based on the national CardioVascular Risk Management (CVRM), written by the Dutch Institute of Health Care Improvement and the Dutch College of General Practitioners (NHG).[9] Concerning primary prevention, the Dutch CVRM uses dedicated prediction charts, based on Dutch prospective cohort studies, to calculate the ten-year risk of cardiovascular morbidity or mortality (ten-year CVD risk). This ten-year CVD risk is stratified as low (< 10%), medium (10-19%), or high (≥ 20%) risk. Patients at high risk with LDL-c levels > 2.5 mmol/l and patients with a total cholesterol/high-density lipoprotein cholesterol (TC/HDL-c) ratio > 8 are all eligible for LLD prescription. LLD treatment is only recommended for patients at medium risk when they present with LDL-c levels > 2.5 mmol/l and one or more additional risk factors (sedentary lifestyle, positive family history of premature CVD, obesity and renal failure). Concerning secondary prevention, patients with myocardial infarction and those who have undergone coronary surgery should be treated. The same holds true for those who have suffered from stroke or peripheral vascular disease and have LDL-c levels > 2.5 mmol/l (*table 1*).

International guidelines were recently compared by Saraf *et al.*[10] Overall, the Dutch guidelines are quite similar to the international guidelines; however, there are some differences. While most international guidelines recommend statin treatment if LDL-c levels are ≥ 4.9 mmol/l, the Dutch CVRM does not include this. The CVRM guideline is unique in its recommendation for treatment in patients with a medium ten-year CVD risk in combination with additional risk factors.

To tackle undertreatment, the NHG is dedicated to improving implementation of these guidelines through developing e-learning modules, organising courses, and generating protocols for nurse practitioners, brochures and websites for patients. The Dutch Heart Foundation has also developed standards for managing cardiovascular risk factors to improve implementation. To improve the awareness of cardiovascular risk in the general population a National Cholesterol test was initiated in 2014.

In the current study, we evaluated the use of LLD in both primary and secondary prevention in a large sample of the Dutch general population (LifeLines study).

METHODS

Study design and participants

LifeLines is an observational population-based study of the Northern provinces of the Netherlands.[11] The study protocol was approved by the medical ethics committee of the University Medical Centre Groningen. All participants provided written informed consent.

For the current study, baseline data were available of 70,292 participants who were recruited between 2006 and 2012. Participants were excluded if data to calculate the ten-year CVD risk were missing or when medication use was not verified. Individuals who reported a myocardial infarction, stroke, or coronary revascularisation procedures, defined as coronary angioplasty or bypass,

Table 1. *Indication to prescribe lipid-lowering drugs based on the Dutch Cardiovascular Risk Management guideline*

Patient characteristic	LDL-c level threshold	Additional criteria
Primary prevention		
Medium 10-year CVD risk	> 2.5 mmol/l	Additional risk factors*
High 10-year CVD risk	> 2.5 mmol/l	All
TC/HDL-c ratio > 8	All	All
Secondary prevention		
Coronary surgery	All	All
Myocardial infarction	All	All
Stroke	> 2.5 mmol/l	All
Peripheral vascular disease	> 2.5 mmol/l	All

* Additional risk factors are classified as renal failure, sedentary lifestyle, obesity, and positive family history of premature CVD. TC/HDL-c ratio = total cholesterol/high-density lipoprotein cholesterol ratio.

were classified as secondary prevention. The remainder were classified as primary prevention. Peripheral vascular disease was not addressed in the LifeLines questionnaires and could unfortunately not be evaluated.

Questionnaires and physical examination

Baseline questionnaires included questions on demographics, family structure, medical history, lifestyle factors and medication use. For the current study, statins and ezetimibe were grouped as LLD. The use of fibrates was not taken into consideration for the current study because fibrates are not the first-choice treatment to lower LDL-c levels. All participants visited the LifeLines research site for physical examination, which included measurement of blood pressure (ten times using an automated blood pressure monitor; Dinamap), body height and weight. Hypertension was defined as systolic or diastolic blood pressure higher than 140 or 90 mmHg, respectively. Positive family history was defined as a parent or sibling who suffered from premature CVD (before the age of 50 years). Sedentary lifestyle was defined as less than 30 minutes of physical activity a day. Estimated glomerular filtration rate (eGFR) was determined using the Cockcroft-Gault formula. Fasting blood samples were collected. Total cholesterol and LDL-c levels were measured with a direct assay (Roche Modular P, Mannheim, Germany). High-density lipoprotein cholesterol (HDL-c) was measured via a direct quantitative assay (Roche Modular P, Mannheim, Germany). Triglycerides were measured using an enzymatic colorimetric test (Roche Modular P, Mannheim, Germany).

Recommendation for treatment and assessment of CVD risk

The CVRM guideline was used to decide whether or not participants were eligible for using LLD. The ten-year risk of cardiovascular morbidity or mortality of each participant was calculated using a risk prediction score according to the CVRM guideline.[9] This algorithm used gender, age, smoking status, systolic blood pressure and TC/HDL-c ratio as the main risk determinants. The risk of participants with rheumatoid arthritis and diabetes mellitus was calculated by adding 15 years to the actual age.[9] The ten-year risk of cardiovascular morbidity or mortality was stratified as low (< 10%), medium (10-19%), or high (≥ 20%) risk.

Statistical analyses

For statistical analysis PASW Statistics (Version 20, IBM, Armonk, NY, USA) was used. Participants' baseline characteristics were presented by mean, standard deviation (SD) and ranges or by percentages in case of categorical variables. We assessed which individuals should receive LLD according to the CVRM guideline. Recommended treatment was compared with the self-reported treatment. For both primary and secondary prevention, differences between those reporting and not reporting LLD treatment were compared using a Student's t test or Mann-Whitney U test. We further explored undertreatment in different subgroups. All statistically significant subgroups in univariate logistic regression (data not shown) were assessed in subsequent multivariate logistic regression, adjusted for sex and age, to analyse independent predictors of not reporting LLD.

RESULTS

Baseline characteristics of study cohort

The study population consisted of 70,292 participants. Baseline characteristics are shown in *table 2*. Briefly, the

Table 2. *Baseline characteristics of study cohort*

Baseline characteristics of 70,292 participants	
Classical risk factors, mean (SD) and [range] or n (%)	
Age (years)	45 (12) [18 – 93]
Total cholesterol (mmol/l)	5.0 (1.0) [1.8 – 14]
Low-density lipoprotein cholesterol (mmol/l)	3.2 (0.9) [0.3 – 11.4]
High-density lipoprotein cholesterol (mmol/l)	1.5 (0.4) [0.1 – 4.0]
Triglycerides (mmol/l)	1.2 (0.8) [0.01 – 23]
Systolic blood pressure (mmHg)	126 (15) [71 – 258]
Gender (male)	31.439 (45)
Current smoker	15.206 (22)
Diabetes mellitus	1209 (1.7)
Rheumatoid arthritis	1263 (1.8)
Additional risk factors, mean (SD) or n (%)	
Body mass index (kg/m^2)	26 (4.2) [14 - 60]
Positive family history of cardiovascular disease	4002 (8.6)
Sedentary lifestyle	2758 (3.9)
Other characteristics, n (%)	
Hypertension	13.138 (19)
Statin treatment	3172 (4.5)
Coronary revascularisation	744 (1.1)
Self-reported myocardial infarction	586 (0.8)
Self-reported stroke	422 (0.6)

Positive family history is defined as a parent or sibling who suffered from CVD before age of 50. Sedentary lifestyle is defined as less than 30 minutes of physical activity a day. SD = standard deviation.

mean age of the participants was 45 (18-93) years and 45% were male. Of the participants, 22% smoked or had stopped smoking in the six months preceding completion of the questionnaire, while 19% of the participants had hypertension. A total of 68,954 participants did not report CVD or stroke. Of these, 92% (n = 63,393) were at low ten-year CVD risk, and 4.2% (n = 2926) and 3.8% (n = 2635) were at medium and high risk, respectively. A total of 1338 participants reported a previous CVD event, i.e. 744, 586 and 386 reported coronary surgery or suffered from myocardial infarction or stroke, respectively. Of note, some patients reported to have suffered from several forms of CVD and therefore the numbers do not add up directly.

Lipid-lowering drugs and primary prevention

Of the participants without CVD (n = 68,954), 3268 (4.7%) were eligible for LLD. The baseline characteristics of these patients are shown in *table 3*. Of these, 77% (n=2515) did not report LLD, which was associated with significantly higher median TC (5.9 vs. 4.5 mmol/l; $p < 0.001$) and median LDL-c (3.9 vs. 2.6 mmol/l; $p < 0.001$) levels, compared with those reporting LLD use. Those who reported use of LLD had a higher BMI (29 vs. 28 kg/m^2; $p < 0.001$) whereas systolic blood pressure was not statistically different (143 vs. 144 mmHg; $p = 0.07$). These results thus indicate that 2515 of 68,954 (3.6%) participants were not using LLD while the guidelines recommended this. Thus, eight out of ten patients eligible for LLD did not report using LLD.

Table 3. *Lipid-lowering treatment for primary prevention*

Characteristics	Recommended to use LLD n = 3268	Reported use of LLD n = 753 (23%)	Reported not using LLD n = 2515 (77%)	P-value
Classical risk factors, mean (SD) or n (%)				
Age (years)	67 (10)	69 (7.3)	67 (11)	<0.001
Total cholesterol (mmol/l)	5.6 (1.2)	4.5 (1.0)	5.9 (1.0)	<0.001
LDL-c (mmol/l)	3.6 (1.0)	2.6 (0.9)	3.9 (0.9)	<0.001
HDL-c (mmol/l)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	ns
Triglycerides (mmol/l)	1.8 (1.7)	1.6 (1.2)	1.8 (1.9)	<0.01
Systolic blood pressure (mmHg)	144 (18)	143 (17)	144 (18)	0.07
Male	2079	420 (20)	1659 (80)	<0.001
Female	1189	333 (28)	856 (72)	<0.001
Current smoker	717	126 (18)	591 (82)	<0.001
Diabetes mellitus	506	341 (67)	165 (33)	<0.001
Rheumatoid arthritis	401	79 (20)	322 (80)	ns
Additional risk factors, mean (SD) or n (%)				
Body mass index (kg/m^2)	28 (4.3)	29 (4.6)	28 (4.1)	<0.001
Positive family history CVD	312	50 (16)	262 (84)	<0.01
Sedentary lifestyle	156	27 (17)	129 (83)	0.08
Other characteristic (n (%))				
Hypertension	2046	460 (22)	1586 (78)	ns
Individuals with low, medium and high risk, n (%)				
Low CVD risk	247	9 (3.6)	238 (96)	<0.001
Medium CVD risk	518	109 (21)	409 (79)	ns
High CVD risk	2503	635 (25)	1868 (75)	<0.001

Positive family history is defined as a parent or sibling who suffered from CVD (before age of 50). Sedentary lifestyle is defined as less than 30 minutes of physical activity a day. LLD = lipid-lowering drugs; LDL-c = low-density lipoprotein cholesterol; HDL-c = high-density lipoprotein cholesterol; CVD = cardiovascular disease; SD = standard deviation.

Subgroup analyses showed that 80% of the males and 72% of the females were not treated according to the CVRM guidelines. The percentage of undertreatment of patients with diabetes mellitus was much lower, namely 32% (*figure 1*).

Lipid-lowering drugs and secondary prevention

A total of 1338 participants reported to have suffered from CVD or stroke. Of these, 36 patients suffered from stroke but had LDL-c levels ≤ 2.5 mmol/l and therefore had no indication for using LLD. Thus 1302 individuals were eligible for treatment. Of these patients, 403 (31%) did not report use of LLD. *Table 4* shows the baseline characteristics of the patients with CVD, who according to the guidelines should receive LLD. The use of LLD in this group was again associated with a significantly lower median TC (5.3 vs. 4.2 mmol/l; $p < 0.001$) and median LDL-c (3.5 vs. 2.4 mmol/l; $p < 0.001$) levels, compared with those who did not report LLD, respectively. Thus, out of ten patients eligible for LLD, three did not use LLD.

While 26% of the men were not treated according to guidelines, this percentage was significantly higher in females (42%; $p < 0.001$). Remarkably, 53% of the patients with stroke and LDL-c levels > 2.5 mmol/l did not report the use of LLD. In contrast, diabetes mellitus, coronary revascularisation and myocardial infarction were associated with the most frequent use of LLD (80-85%) (*figure 1*).

Multivariate logistic regression analysis

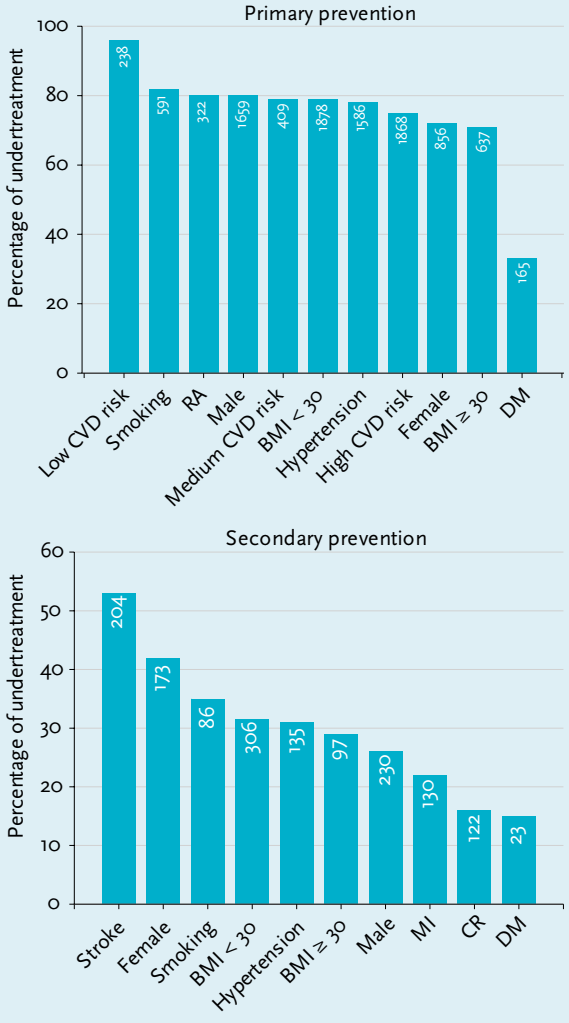
The risk factors for undertreatment of LLD, based on multivariate logistic regression analysis, for primary and secondary prevention are shown in *table 5*. The strongest predictor of not reporting LLD use was a low ten-year CVD risk (OR = 2.4; $p = 0.03$). These were individuals with TC/HDL-c ratio > 8. Patients with diabetes mellitus, females, older patients and those with higher BMI were more likely to receive LLD (OR < 1.0; $p < 0.05$).

For secondary prevention, the strongest predictor of undertreatment was being female (OR = 1.63; <0.01). Predictors of LLD treatment following the guidelines are coronary revascularisation, diabetes mellitus, myocardial infarction, higher BMI and higher age (OR < 1.0; $p < 0.05$).

DISCUSSION

This general population study in the Netherlands showed that, despite clear recommendations, 77% of subjects at high risk of CVD (primary prevention) and 31% with CVD (secondary prevention) did not report receiving LLD. Although these rates of undertreatment have been reported previously, this large and recent study indicates that better action should be taken by healthcare providers and policy makers in the Netherlands.

Figure 1. *Percentage of undertreatment of individuals eligible for LLD treatment in different subgroups for primary (top) and secondary (bottom) prevention. Numbers on top of the bar are the total number of participants undertreated in the subgroup. LLD = lipid-lowering drug; RA = rheumatoid arthritis; MI = myocardial infarction; CR = coronary revascularisation*



Primary prevention

According to the CVRM guideline, 4.7% (n = 3268) of the LifeLines subjects without CVD, but with high cardiovascular risk, should have been treated with LLD. Only 23% actually reported using LLD. In a previous study of the general Dutch population, published in 2003, (MORGEN project, n = 61,918; aged 20-59 years), 3.8% were eligible to use LLD.[4] Since LDL-c and TC levels increase with age, the higher percentage in our study can be attributed by the inclusion of participants over 59 years of age. In addition, we studied individuals at overall risk of CVD, whereas the MORGEN project focused on hypercho-

Table 4. *Lipid lowering treatment in patients for secondary prevention*

Characteristics	Recommended to use LLD n = 1302	Reported use of LLD n = 899 (69%)	Reported not using LLD n = 403 (31%)	P-value
Classical risk factors, mean (SD) or n (%)				
Age (year)	63 (12)	65 (10)	58 (15)	<0.001
Total cholesterol (mmol/l)	4.5 (1.0)	4.2 (0.8)	5.3 (0.9)	<0.001
LDL-c (mmol/l)	2.8 (0.9)	2.4 (0.7)	3.5 (0.8)	<0.001
HDL-c (mmol/l)	1.3 (0.4)	1.3 (0.4)	1.4 (0.4)	<0.001
Triglycerides (mmol/l)	1.4 (0.8)	1.4 (0.8)	1.4 (0.8)	ns
Systolic blood pressure (mmHg)	133 (18)	133 (17)	134 (19)	ns
Male	890	660 (74)	230 (26)	<0.001
Female	412	239 (58)	173 (42)	<0.001
Current smoker	249	163 (65)	86 (35)	ns
Diabetes mellitus	152	129 (85)	23 (15)	<0.001
Rheumatoid arthritis	72	51 (71)	21 (29)	ns
Additional risk factors, mean (SD) or n (%)				
Body mass index (kg/m^2)	28 (4.1)	28 (3.9)	27 (4.4)	<0.01
Positive family history CVD	67	49 (73)	18 (27)	ns
Sedentary lifestyle	46	30 (65)	16 (35)	ns
Other characteristics, n (%)				
Hypertension	437	302 (69)	135 (31)	ns
Myocardial infarction	586	456 (78)	130 (22)	<0.001
Stroke	386	182 (47)	204 (53)	<0.001
Coronary revascularisation	744	622 (84)	122 (16)	<0.001

Positive family history is defined as a parent or sibling who suffered from CVD before the age of 50. Sedentary lifestyle is defined as less than 30 minutes of physical activity a day. LLD = lipid-lowering drugs; LDL-c = low-density lipoprotein cholesterol; HDL-c = high-density lipoprotein cholesterol; CVD = cardiovascular disease; SD = standard deviation.

lesterolaemia. It is interesting to note, however, that in the MORGEN project, adherence to guidelines was 20% compared with 23% in the current study, which indicates only a slight improvement over the last ten years.

The most obvious reason for the marked undertreatment in our study is the possibility that participants may have never been tested for ten-year CVD risk. Since the most important parameters needed to assess CVD risk (i.e. age, smoking habits, blood pressure, and gender) are easy to obtain, insufficient awareness on the part of the individuals and/or their physicians of CVD risk likely contributed to the observed undertreatment.[12]

We further assessed whether we could identify subgroups that were prone to undertreatment. Of the patients with diabetes mellitus, 67% reported LLD which is probably related due to the more intense medical care, thus monitoring of plasma lipid levels, in these individuals. In the USA, 52% of individuals with diabetes older than 40 years reported statin use.[8] Multivariate logistic regression analysis showed that undertreatment in the LifeLines study was most apparent in younger participants, males, those with lower BMI, and low ten-year CVD risk.

Secondary prevention

Of the patients who suffered from CVD and had a clear indication for LLD, only 69% reported to be actually treated. In EUROASPIRE III,[13] very similar data but on a much smaller dataset were reported: 115 out of 167 (69%) Dutch participants reported LLD. Other data collected in the Netherlands in 2007 showed that 53% of the CVD patients were undertreated,[14] suggesting a small improvement.

Table 5. *Risk factors for undertreatment of LLD based on multivariate logistic regression analysis for primary and secondary prevention*

Variable	OR	95% CI	P-value
Primary prevention			
Low risk (< 10%)	2.40	1.08-5.27	0.03
Age, per year	0.98	0.96-0.99	<0.01
Body mass index, per kg/m²	0.95	0.93-0.98	<0.001
Gender, female	0.80	0.65-0.98	0.02
Diabetes mellitus	0.10	0.08-0.12	<0.001
Positive family history	1.29	0.89-1.86	ns
High risk (> 20%)	0.75	0.55-1.04	ns
Secondary prevention			
Gender, female	1.63	1.23-2.18	<0.01
Age, per year	0.96	0.95-0.97	<0.001
Body mass index, per kg/m²	0.96	0.93-0.99	0.01
Myocardial infarction	0.59	0.40-0.85	<0.01
Diabetes mellitus	0.45	0.27-0.74	<0.01
Coronary revascularisation	0.21	0.14-0.31	<0.001
Stroke	0.85	0.53-1.36	ns

In line with other Dutch studies,[5] the current study shows that for secondary prevention 42% of the females did not report LLD, whereas this was only 26% in males. Although CVD is currently the number one cause of death in women in the Netherlands, it appears clear that general practitioners underestimate the risk of CVD in women.[15]

Our results furthermore show that of the patients who reported stroke, 53% were not reporting LLD use. Remarkably, undertreatment of patients with stroke is even worse in the Oslo Heart study: only 21% of men and 16% of the women were using LLD at age 60, while at age 70 these numbers increased to 44% and 48%, respectively.[3] In another Dutch population study it was shown that only 10% of patients with cerebrovascular accident/transient ischaemic accident were undertreated.[14] The heterogeneity of these findings may be related to differences in mean age in the respective studies as older people are much more likely to receive a statin. Nevertheless, our observations that both stroke and female gender are associated with undertreatment may need attention in the Netherlands, especially since women generally have a higher overall risk of stroke.[16] Multivariable logistic regression analysis showed that physicians prescribing LLD should additionally focus on females and individuals at a younger age.

Limitations

The LifeLines questionnaires do not assess peripheral vascular disease, and we could not account for this parameter in our secondary prevention analysis. Next, the information on medication was dependent on the information given by participants. Furthermore, our dataset lacked information on BMI (n = 15), eGFR (n = 262), daily activity (n = 5530) and family history of CVD (n = 23,850). Since these determinants were used in the decision for LLD treatment in the medium ten-year CVD category, this may have resulted in an underestimation of the number of participants with an indication for LLD. We had to decide how to use the guidelines for those patients who had LDL-c levels ≤ 2.5 mmol/l and reported LLD use. We have assumed that these participants had LDL-c levels > 2.5 mmol/l before initiation of LLD treatment, which may have led to overestimating the proportion of proper recommended treatment.

The CVRM guideline used in this study was published in June 2011. However, the inclusion of the LifeLines participants started in 2006 indicating that a significant number of participants entered in a time period in which the previous guideline was applicable. Although the differences between the guidelines are small, the CVRM 2011 guidelines do recommend more aggressive treatment of patients with rheumatoid arthritis. As a result, 145 patients with rheumatoid arthritis were wrongly categorised. This did not affect the overall outcome of our primary prevention analysis (this is only 4.4% of total patients eligible for LLD treatment in primary prevention). In line, *table 5* shows that rheumatoid arthritis was not a significant predictor of undertreatment in our multivariate analysis. However, due to the change in the guidelines during the course of our study, the outcome of our study is not applicable for patients with rheumatoid arthritis.

As Lifelines is a population-based study, it should be mentioned that the Dutch CVRM guidelines do not advocate the assessment of a cardiovascular risk profile in all adults. Reasons to assess this are e.g. the presence of hypertension, family history with premature CVD or diabetes. Looking into this specifically, we found however that 90% of participants who were eligible to use LLD, also met criteria for assessing a cardiovascular risk profile (data not shown).

Conclusions and perspective

This large population-based study showed that 77% of the individuals, without CVD, in the Northern three provinces of the Netherlands did not receive LLD while the CVRM guideline would recommend this. This figure is 31% for secondary prevention. While significant progress in the treatment of CVD has previously been reported, our current data showed no signs of further improvement over the last years in the Netherlands.

The results of this study call for improved awareness and better treatment. The development of simple apps to estimate ten-year CVD risk could be of help. However, unfortunately, several key parameters such as plasma levels of HDL-c and LDL-c as well as systolic blood pressure, are currently needed to accurately estimate ten-year CVD risk. Clearly, our data call for large-scale primary prevention programs to improve awareness and treatment of CVD.

DISCLOSURES

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ORIGINAL ARTICLE

Favourable SVR12 rates with boceprevir or telaprevir triple therapy in HIV/ HCV coinfected patients

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ABSTRACT

Background: Recent publications have reported superior efficacy of telaprevir- or boceprevir-based triple therapy over conventional peginterferon-alfa/ribavirin therapy, albeit with varying rates of adverse events and treatment discontinuations in HIV/ HCV coinfected patients. Therefore, the aim of this study is to describe the effectiveness of triple therapy in an HIV/HCV coinfection cohort in the Netherlands.

Methods: HIV-infected patients with chronic HCV genotype 1 starting triple therapy including either boceprevir or telaprevir were enrolled, 26% had F3-F4 fibrosis. Data were assessed at Week 4, 8, 12, 24, 48 and SVR12 (i.e. absence of detectable plasma HCV RNA 12 weeks after completion of treatment). Failure was defined as discontinuation of treatment due to virological failure, adverse events or loss to follow-up.

Results: A total of 53 HIV/ HCV coinfected patients started peginterferon-alfa/ribavirin therapy with either boceprevir (n = 29) or telaprevir (n = 24). SVR12 was achieved in 19 (66%) of the boceprevir-treated and 15 (63%) of the telaprevir-treated patients. Both prior relapse and achievement of a rapid virological response were associated with a higher SVR12 rate. Non-response, breakthrough and relapse occurred in 4, 1 and 5 patients on boceprevir and 3, 2, 2 on telaprevir, respectively. One patient was lost to follow-up and one patient died due to progression of liver failure. Except for these two patients, no treatment discontinuations were observed due to adverse events.

Conclusion: In HIV/ HCV coinfected patients, boceprevir or telaprevir triple therapy was well tolerated and resulted in favourable SVR12 rates comparable with previous publications concerning HCV mono-infected patients.

KEYWORDS

Boceprevir, direct-acting antiviral agents, hepatitis C, HIV, pegylated interferon-alfa, telaprevir

INTRODUCTION

The introduction of direct-acting antiviral agents (DAA) for the treatment of hepatitis C virus (HCV) infection

heralded a whole new era of treatment possibilities with agents directed at multiple HCV targets (i.e. NS3, NS5A and NS5B).[1] However, the speed of these developments has not been balanced by reimbursement policies which differ among countries.[2] While in some countries interferon-free regimens with sofosbuvir and daclatasvir or simeprevir are now the standard of care, in many others first-generation protease inhibitors telaprevir and boceprevir are still the only available DAAs. Moreover, most middle- to high-income countries restrict the use of these new DAAs to those most in need: patients with advanced fibrosis, cirrhosis or extrahepatic manifestations.

Addition of boceprevir or telaprevir to peginterferon-alfa (pegIFN-alfa) plus ribavirin has led to increased sustained virological response rates (SVR) of 65-75% for HCV mono-infected patients.[3,4] Since HCV and the human immunodeficiency virus (HIV) are partly transmitted along similar routes, coinfection frequently occurs ranging from around 30% in men having sex with men to as high as 80% in injection drug users.[5] In the Netherlands, around 10% of HIV-infected patients are coinfected with HCV.[6] In these HIV/HCV coinfected patients, SVR rates with pegIFN-alfa and ribavirin have traditionally been lower compared with those achieved in HCV mono-infected patients.[7,8] To date, only two small phase-2 studies and three cohort studies have been published showing similar efficacy of boceprevir and telaprevir in combination with pegIFN-alfa/ribavirin in HIV/HCV coinfected patients when compared with HCV mono-infected patients.[9-13] However, varying rates of adverse events and treatment discontinuations due to differences in study populations (i.e. numbers of patients with cirrhosis and Caucasians) were reported in HIV/HCV coinfected patients.[14] Furthermore, these cohort studies suffered from selection bias since mostly patients from early access or compassionate use programs were included. Extending the knowledge on treatment outcomes of boceprevir- and telaprevir-based therapy in HIV/HCV coinfected patients remains important for two reasons. First, despite the introduction of more novel direct-acting agents, boceprevir and telaprevir are still used in many countries around the world due to financial restrictions. Second, to confirm that boceprevir and telaprevir have similar effectiveness in HIV/HCV coinfected patients compared with HCV mono-infected patients. Here, we report the Dutch experience with boceprevir and telaprevir in a cohort of HIV/ HCV coinfected patients.

METHODS

Patients

From the Netherlands ATHENA HIV observational cohort registry, maintained by the HIV Monitoring Foundation (HMF),[15] we selected all HIV-positive patients coinfected with chronic HCV genotype 1 of 18 years and older who were treated for 12 weeks or more with pegIFN-alfa/ ribavirin plus telaprevir or plus boceprevir between August 2010 and April 2013. Clinical visits included in this study were start of treatment (week 0), week 4, week 8 (for those with a pegIFN-alfa/ribavirin lead-in before boceprevir), week 12, week 24, week 48 (end of treatment) and week 12 follow-up (to assess SVR12, i.e. HCV RNA undetectable 12 weeks after the end of treatment). Data on sociodemographic characteristics and on HIV/HCV-related and haematological parameters together with reasons for treatment discontinuation were obtained from the registry. All patients within the ATHENA cohort gave consent (via an opt-out procedure) for their anonymised data to be collected and stored in a central database as part of their routine HIV care. A research proposal to perform the current study was submitted to and approved by the HMF working group.

Treatment

The standard duration of treatment was 48 weeks, while shortening to 24 (28 with boceprevir) or 36 weeks occurred based on clinical criteria at the treating physician's discretion. Triple therapy was given with pegIFN-alfa 2a (180 µg weekly) or 2b (1.5 µg/kg weekly) together with weight-based ribavirin 1000-1200 mg daily (in two divided doses). Boceprevir was dosed orally at 800 mg three times a day (TID) taken with food for a duration of 24 to 44 weeks after a 4-week pegIFN-alfa/ ribavirin lead-in phase.[16] Telaprevir was administered orally at doses of 750 mg TID in most patients while one patient received 1125 mg twice daily (BID) and another patient took 1125 mg TID because of a combination with efavirenz.[17] Futility rules and treatment duration were as prescribed by the package insert of boceprevir and telaprevir, and in accordance with international treatment guidelines.[18-20]

Severe liver fibrosis was defined as F3 or F4 by METAVIR classification on preceding liver biopsy or by liver stiffness measurement (Fibroscan, Echosens, Paris, France), using a cut-off value of 12.5 kPa or higher.

HCV RNA determination and definitions of response

Plasma HCV RNA was quantified at the local hospitals with their respective polymerase chain reaction assay (COBAS Ampliprep/COBAS TaqMan V2.0, Roche Nederland B.V., Woerden, the Netherlands: detection limit 15 IU/ml; Abbott RealTime HCV, Chicago, USA: detection limit 12 IU/ml).

A rapid virological response (RVR) was defined for telaprevir as an undetectable HCV RNA at week 4 of triple therapy whereas RVR for boceprevir-based therapy was defined by HCV RNA undetectability at week 8 of treatment.

Non-response to telaprevir was defined as plasma HCV RNA > 1000 IU/ml at week 4 or 12 during treatment while non-response to boceprevir was defined as plasma HCV RNA > 100 IU/ml at week 12 or detectable HCV RNA at week 24 of treatment. Relapse for both treatments was concluded when HCV RNA became detectable after being undetectable at the previous measurement.

Response to previous (pegylated) interferon-alfa/ ribavirin therapy was defined by classical definitions for non-response/ relapse as published in international guidelines.[18,20]

Statistical analysis

Data were analysed using descriptive statistics with continuous variables expressed as median with interquartile range, and categorical variables as numbers with percentages. Mann-Whitney test was used for continuous variables while Fisher's exact and Kruskal-Wallis test was performed for categorical variables. An intent-to-treat analysis was used calculating loss to follow-up, deceased or discontinuation due to adverse events as treatment failures. The primary endpoint of this study was SVR12. Data were analysed using Graphpad Prism V5 for Mac (San Diego, California, USA).

RESULTS

Study population

A total of 53 HIV/HCV coinfected patients, 45 men and 8 women, were included in this study (*table 1*) with a median age at the start of HCV treatment of 47 years (IQR 44-56). Two-thirds of the cohort were infected with HCV genotype 1a and 26% had severe liver disease (F3 or F4). Regulative

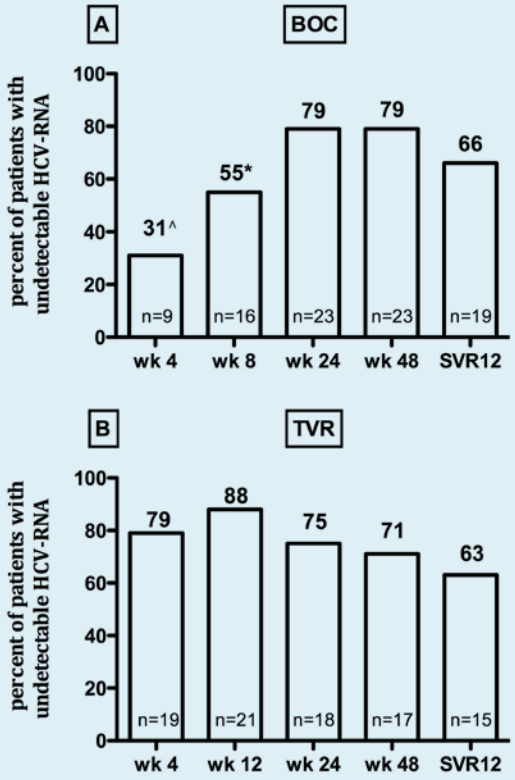
Table 1. *Patient characteristics at time of treatment initiation*

Patients	All (n = 53)	BOC (n = 29)	TVR (n = 24)	p-value ¥
Age (years)	47 (44-56)	47 (44-56)	49 (45-53)	0.90
Male gender, no. (%)	45 (85%)	23 (79%)	22 (92%)	0.27
Origin - Netherlands - Rest of Europe - South America - North Africa/ Central Asia - South-East Asia - Unknown	 37 11 1 1 2 1	 20 6 0 1 2 0	 17 5 1 0 0 1	
HCV genotype, no. (%) -1a -1b -Not subtyped	 34 (64%) 5 (9%) 14 (26%)	 18 (62%) 4 (14%) 7 (24%)	 16 (67%) 1 (4%) 7 (29%)	0.48
Duration of HCV-protease inhibitor therapy, weeks		43 (24-44)	12 (12-13)	
HCV RNA log10, no. (IQR)	6.10 (5.64-6.58)	6.13 (5.77-6.37)	5.91 (5.51-6.84)	0.91
Fibrosis stage ± - F0-F2 - F3F4 - Unknown	 35 (66%) 14 (26%) 4 (8%)	 22 (76%) 7 (24%)	 13 (54%) 7 (29%) 4 (17%)	0.52
Prior treatment response - Naive - Non-responder - Relapse	 32 (60%) 12 (23%) 9 (17%)	 19 (66%) 7 (24%) 3 (10%)	 13 (54%) 5 (21%) 6 (25%)	0.68
CD4 /mm3	560 (400-732)	585 (388-743)	512 (413-733)	0.59
HIV RNA <50 copies/ml*	51 (96%)	29 (100%)	22 (92%)	0.20
Raltegravir-containing regimen	38 (72%)	25 (86%)	13 (54%)	0.03

¶ Either median with (IQR) or number with (%) are shown; ¥ difference between boceprevir (BOC) and telaprevir (TVR) groups (Mann-Whitney U or Fisher's exact test); * 2 patients in the TVR group were not treated for HIV at the time of HCV therapy; ± missing data in 4 patients on TVR.

duration of treatment differed for telaprevir and boceprevir, which was also apparent in our study cohort. Telaprevir was prescribed for a median duration of 12 weeks (IQR 12-13 weeks) with pegIFN-alfa/ribavirin continuing until a median of 48 weeks while boceprevir was prescribed for 43 weeks (IQR 24-44) after a 4-week lead-in with pegIFN-alfa/ribavirin. Raltegravir was more frequently used in patients on boceprevir compared with those on telaprevir (86% versus 54%; p = 0.03). Finally, there was no difference in HCV genotypes and baseline HCV RNA between boceprevir- and telaprevir-treated patients.

Figure 1. *Number of patients with undetectable HCV RNA at different treatment time points treated with peginterferon-alfa/ribavirin in combination with boceprevir (A) or telaprevir (B)*



* data missing in 4 patients and ^data missing data for 3 patients. BOC = boceprevir; TVR = telaprevir; SVR12 = sustained virological response at week 12 after treatment discontinuation; wk = week.

Treatment response

SVR12 in boceprevir- and telaprevir-treated patients is depicted in *figure 1A* and *1B* and was achieved by 19 of 29 (66%) and 15 of 24 (63%) patients, respectively. The difference at week 4 of therapy between patients on telaprevir and on boceprevir (HCV RNA week 4 undetectable in 79% and 31% respectively) is explained by the pegIFN-alfa/ribavirin lead-in phase in the latter group (*figure 1A and B*). Virological non-response, breakthrough and relapse rates are shown in *table 2*. Four patients treated with boceprevir and three on telaprevir had a primary non-response on treatment. In the telaprevir group, one patient was lost to follow-up and another patient died 16 weeks after the start of treatment. Although both patients achieved an RVR, according to the intention-to-treat principle, they were regarded as non-responders and treatment failures. Relapse rates were 17% (n = 5) in the boceprevir- and 9% (n = 2) in the telaprevir-treated group (p = 0.44).

Predictors of treatment response

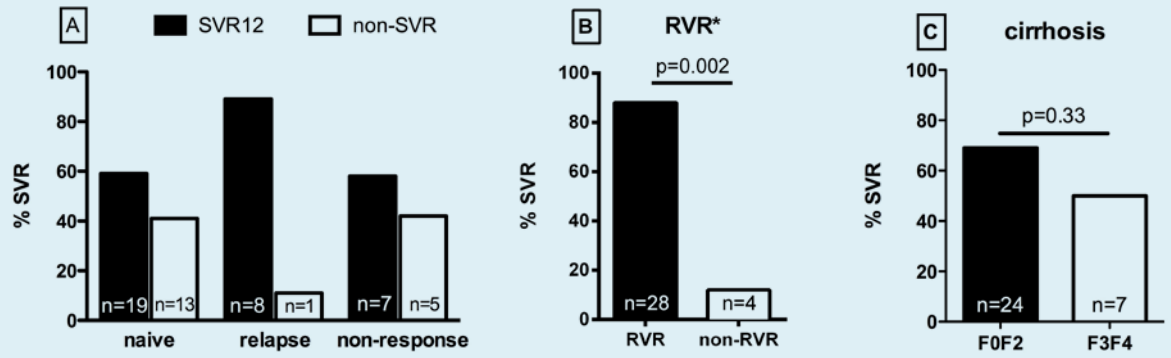
Since patient characteristics and treatment outcomes of boceprevir- and telaprevir-treated patients were comparable, we analysed predictive factors for treatment success in the overall study population. Patients with relapse after a previous course of pegIFN-alfa/ribavirin therapy had the highest SVR12 rates of 89% (8 out of 9 patients) followed by previous non-responders (64%; 7 of 11) and HCV-therapy naïve patients (59%; 19 of 32) (*figure 2A*). RVR was achieved in 35 of 53 (66%) patients of whom 28 (88%) went on to achieve an SVR12 (p = 0.002) (*figure 2B*). In contrast, four patients without an RVR still managed to reach SVR12. Sixteen of 25 (64%) boceprevir-treated

Table 2. *Number of patients at each time point with virological failure during either BOC or TVR treatment*

	BOC (n = 29)			TVR (n = 24)		
	Non-response	Breakthrough	Relapse	Non-response	Breakthrough	Relapse
Week 12	4	0	0	3	0	0
Week 24	0	1	1	0*	2	0
Week 48	0	0	0	0	0	0
SVR12	0	0	4	0	0	2
Total no. of patients	10 (34%)			9 (37%)		

*1 patient lost to follow-up and 1 patient who died at week 16 were regarded as treatment failures in the analysis.

Figure 2. *SVR12 stratified by prior treatment response (A), RVR achievement (B) and cirrhosis (C) Categories naive, relapse and non-response on the X-axis were observed in previous therapy; for patients on BOC-containing triple therapy, RVR was determination at week 8; * missing data for 4 patients*



patients and 19 of 24 (79%) telaprevir-treated patients achieved an RVR (p = 0.35).

Treatment was shortened in eight of 35 patients with an RVR, two on boceprevir (treated for 28 and 36 weeks) and six on telaprevir (median 24 week (IQR 21-27). Of those, six (75%) subsequently went on to achieve an SVR12 while two patients (one on boceprevir treated for 28 weeks and one on telaprevir treated for 24 weeks) experienced a relapse.

Presence of severe liver fibrosis or cirrhosis did not markedly influence treatment outcome with seven of 14 (50%) of F3-F4 patients reaching SVR12 compared with 24 of 35 (69%) with F0-F2 reaching SVR12 (p = 0.33) (*figure 2C*). Finally, other factors such as HCV genotype, baseline HCV RNA, CD4 cell count and ethnic origin were not associated with treatment outcome (data not shown).

Safety of treatment

Boceprevir- and telaprevir-based therapies were generally well tolerated with recorded symptoms being malaise, diarrhoea and dizziness. Except for two patients, no severe adverse events leading to treatment discontinuation were noted in the ATHENA database. One patient was hospitalised for reasons not related to the telaprevir-containing triple therapy and subsequently achieved an SVR12. Another patient with Child-Pugh C (MELD-Na score of 40), baseline platelets of 75 x 10^9/l and an albumin level of 28 g/dl, died 16 weeks after the start of treatment with pegIFN-alfa/ribavirin and telaprevir due to complications of liver cirrhosis (i.e. spontaneous bacterial peritonitis with subsequent hepatic encephalopathy and hepatorenal syndrome).

Haemoglobin measurements at baseline, week 4 and week 12 were available in 48 patients (89%). The median baseline haemoglobin was 9.2 mmol/l (14.8 g/dl), which dropped to a median of 1.4 mmol/l (0.6 g/dl) after 4 weeks and 2.7 mmol/l (4.3 g/dl) after 12 weeks, respectively (p < 0.0001). Erythropoietin was prescribed in four (8%) patients while no patients discontinued therapy because of severe anaemia. Dose reduction of 200 mg ribavirin daily was done in six patients including those on erythropoietin therapy.

Two patients (one on boceprevir and one on telaprevir) experienced severe anaemia which in one patient contributed to non-compliance, resulting in viral breakthrough, while the other patient decided to stop therapy with subsequent viral relapse (*table 2*). Two other patients, both treated with telaprevir and achieving an SVR12, experienced leukopenia for which a pegINF-alfa dose reduction was applied.

Despite adequate antiviral drug concentrations, one patient developed HIV viral breakthrough at week 16 during anti-HCV therapy. His antiviral regimen was changed from atazanavir/ritonavir/raltegravir/maraviroc to darunavir/ritonavir/maraviroc with subsequent HIV RNA undetectability. However, at week 24 of anti-HCV therapy his HCV RNA was again detectable (i.e. relapse). All other patients were HIV undetectable during the course of their anti-HCV therapy.

DISCUSSION

The outcome of boceprevir- and telaprevir-based triple therapies in HIV/HCV coinfected patients in 'real-life' is favourable and these results are comparable with SVR data previously obtained in clinical trials and early access programs in both HCV mono-infected and HIV/HCV coinfected patients.[3,4,10,11] Furthermore, this study again confirms that patients with a relapse on previous (peg) IFN-alfa/ribavirin therapy have a high chance of achieving treatment success on these triple therapies.[21,22] This latter observation has consistently been reported among other

boceprevir- or telaprevir-treatment studies without a clear explanation. It could be that since previous relapsers on pegIFN-alfa/ribavirin therapy have been exposed to these modalities, they know what to expect from treatment and therefore have a better tolerance or adherence.

The phase-3 clinical trials with boceprevir or telaprevir in combination with peg-IFN-alfa/riba performed in HIV/ HCV coinfected and HCV mono-infected patients reported comparable SVR12 rates of around 65%-75%.[3,4,10,11] This is higher than previously achieved with pegIFN-alfa/ribavirin therapy with SVR24 rates between 17-36% for HCV genotype 1 in HIV/HCV coinfected patients.[23-25] In contrast, with the high efficacy of new interferon-free regimens with around 90% SVR rates there is no difference in outcome (SVR12) between HIV/ HCV coinfected and HCV mono-infected patients.[26] However, efficacy of triple therapy reported from early access and real-life cohorts in HIV/ HCV coinfected patients varied due to differences in included patients. For example, the CUPIC cohort and other more recently published cohorts reported SVR12 rates between 40%-55% for boceprevir and telaprevir in treatment-experienced and/ or cirrhotic HCV mono-infected patients.[27-29] Other studies have, however, reported higher SVR rates of around 61%-80% in similarly affected HIV/HCV coinfected patients.[9,13] Our study is distinctive since it describes a relatively healthy, in majority HCV therapy naive, population with only a small proportion of cirrhotic patients. Moreover, the Dutch HIV healthcare system is concentrated in a few specialised treatment centres with highly trained infectious diseases and HIV nurses. This might explain the low number of severe side effects and low drop-out rate seen in our cohort. However, one patient with cirrhosis died after reaching 16 weeks of therapy while being HCV RNA undetectable. This patient's baseline platelet count and albumin were 75 x 10^9/l and 28 g/dl, respectively, which in the CUPIC cohort were found to be associated with an increased risk of death.[27] On this basis, triple therapy with either boceprevir or telaprevir is contraindicated in those patients with a low albumin and low platelet count. Furthermore, probably due to a relatively small sample size, treatment outcome was not statistically significantly affected by fibrosis stage though a difference in percentage was notable (50% in F3-F4 versus 69% in F0-F2). This is in line with the literature showing that the presence of liver cirrhosis is a negative predictor for outcome of DAA-based therapy.[30]

Considering the long duration of triple therapy in combination with many described side effects of therapy, shortening of therapy might be a possibility in some patients with favourable HCV viral kinetics. Although the number of patients in whom shortening of therapy was performed (at the treating physician's discretion) was small, a favourable outcome especially for those on telaprevir was seen in this study. Similarly, shortening triple therapy from 48 weeks to 24/28 weeks was recently also investigated in the HIVCOBOC-RGT study by Mandorfer *et al.*[31] Although the number of patients in the study was small, a 100% SVR12 rate was reached in those 14 becoming HCV RNA undetectable ('target not detected') at week 8 of therapy (i.e. including the four-week lead-in phase). Moreover, in our study there was one patient on telaprevir lost to follow-up after 16 weeks of therapy who was regarded as a treatment failure. However, this patient had a favourable viral kinetic response with HCV RNA undetectability at week 2 of telaprevir-based triple therapy. Several publications have shown that very short courses of triple therapy are sufficient to achieve an SVR.[32,33] In all, shortening of therapy based on RVR undetectability with similar SVR rates and lower costs of therapy might be a favourable strategy, especially in resource-limited setting.

There are some limitations to this study. Since we collected our data from the Dutch HIV database, certain data regarding severity of fibrosis such as albumin and platelets were not collected the way data were collected in the CUPIC cohort. Finally, there are small differences (though not statistically significant) in baseline characteristics such as fibrosis stage and prior treatment response between patient groups treated with either telaprevir or boceprevir. However, when analysing the data excluding the four patients without data on fibrosis stage, the SVR12 rate dropped to 60%, only marginally lower than for the whole study population. We therefore think that these differences in baseline characteristics did not influence the outcome in this study.

In conclusion, SVR12 rates were favourable for pegIFN-alfa/ribavirin with boceprevir or telaprevir in this relatively healthy cohort of HIV/ HCV coinfected patients and comparable with those in HCV mono-infected patients. Furthermore, although numbers were low, shortening of treatment duration seems feasible in those patients who achieve HCV RNA undetectability at week 4 of therapy.

DISCLOSURES

J.E. Arends: Advisory boards of Janssen, MSD, Abbvie, ViiV, BMS; Speakers Bureau Gilead.

K. Brinkman: Advisory boards of Janssen, MSD, Abbvie, ViiV, BMS, and Gilead.

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P. Reiss: through his institution has received independent scientific grant support from Gilead Sciences, Janssen Pharmaceuticals Inc., Merck&Co, Bristol-Myers Squibb, Boehringer Ingelheim and ViiV Healthcare. In addition he serves on a scientific advisory board for Gilead Sciences and on a data safety monitoring committee for Janssen Pharmaceutica N.V., for which his institution has received remuneration.
C. Richter: advisory board of MSD, BMS, Janssen, Roche and AbbVie.
A.I.M. Hoepelman: Consulting honorarium Janssen, Advisory boards of Janssen, Gilead, BMS, MSD and ViiV.
The other authors declare no conflicts of interest.

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ORIGINAL ARTICLE

What are we waiting for? Factors influencing completion times in an academic and peripheral emergency department

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ABSTRACT

Background: A long completion time in the Emergency Department (ED) is associated with higher morbidity and in-hospital mortality. A completion time of more than four hours is a frequently used cut-off point. Mostly, older and sicker patients exceed a completion time of four hours on the ED. The primary aim was to examine which factors currently contribute to overcrowding and a time to completion of more than four hours on the EDs of two different hospitals, namely: the VU Medical Center (VUmc), an academic level 1 trauma centre and the St. Antonius Hospital, a large community hospital in Nieuwegein. In addition, we compared the differences between these hospitals.

Methods: In this observational study, the time steps in the process of diagnosing and treatment of all patients visiting the EDs of the two hospitals were measured for four weeks. Patients triaged as Emergency Severity Index (ESI) category 2/3 or Manchester Triage System (MTS) orange/yellow were followed more closely and prospectively by researchers for detailed information in the same period from 12.00-23.00 hrs.

Results: In the VUmc, 89% of the patients had a completion time of less than four hours. The average completion time (n = 2262) was 2:10 hours, (median 1:51 hours, range: 0:05-12:08). In the St. Antonius Hospital, 77% of patients had a completion time shorter than four hours (n = 1656). The average completion time in hours was 2:49 (n = 1655, median 2:34, range: 0:08-11:04). In the VUmc, a larger percentage of ESI 1, 2 and 3 patients did not achieve the 4-hour target (14%, 20% and 19%) compared with ESI 4 and 5 patients (2.7% and 0%), $p < 0.001$. At the St. Antonius Hospital, a greater percentage of orange and yellow categorised patients exceeded four hours on the ED (32% and 28%) compared with red (8%) and green/blue (13%), $p < 0.001$. For both hospitals there was a significant dependency between exceeding four hours on the ED and the following: whether a consultation was performed ($p < 0.001$), the number of radiology tests performed ($p < 0.001$), and an age above 65 years.

Conclusion: Factors leading to ED stagnation were similar in both hospitals, namely old age, treatment by more than one speciality and undergoing radiological tests. Uniform remedial measures should be taken on a nationwide level to deal with these factors to reduce stagnation in the EDs.

KEYWORDS

Four hour target, completion times, academic hospital, peripheral hospital

INTRODUCTION

Long completion time in the emergency department (ED) can lead to overcrowding and is associated with negative outcomes, such as increased risk of hospital admission and in-hospital mortality.[1] Therefore, optimising ED patient flow is an important and frequently discussed topic. Because the frequency and type of presentations

are unpredictable, it remains a challenge for emergency physicians and nurses to provide adequate care for all patients, especially during the busiest moments.

Overcrowding and long ED completion times can occur when the maximum available care does not meet increasing demands. A recent study demonstrated that visiting an ED on crowded days resulted in delays in resuscitation efforts and higher in-hospital mortality.[1] Also in discharged patients, it has been noted that a long stay on the ED was associated with increased risk of hospital admission within seven days and mortality.[2] In that light, we previously conducted a study at the VU University Medical Center, Amsterdam, the Netherlands (VUmc), to obtain insight into factors which could contribute to a completion time of more than four hours, and we demonstrated that a vast majority of the patients left the ED within four hours (84%).[3] However, the patients exceeding the four hours were older, sicker and treated by multiple consulting specialists. In addition, after finishing all the diagnostic tests, there was a marked delay until discharge, probably caused by inefficient decision-making by the junior doctors.[3] This study was conducted in a single academic centre only and therefore was not generalisable to community hospitals. For that reason, we decided to conduct a new study in two different hospitals: an academic centre and a large community hospital. The primary aim was to examine which factors currently contribute to overcrowding and completion times longer than four hours on the ED in the VUmc, a level 1 academic trauma centre and on an ED in a large community hospital, the St. Antonius Hospital in Nieuwegein, the Netherlands and whether or not these hospitals encounter the same problems in patient flow on the ED.

MATERIALS AND METHODS

Study design and setting

This prospective study was performed in the EDs of the VUmc and St. Antonius Hospital.

VUmc is an academic urban level 1 trauma centre in Amsterdam with approximately 29,000 ED visits per year. During the study period there were 11 residents in emergency medicine, including seven fellows of emergency medicine and four non-trainees working in shifts. Residents were supervised by four qualified emergency physicians (EPs) and one surgeon. The emergency medicine trainees and EPs belong to the surgical staff. At the ED of the VUmc, all patients presenting themselves without a referral from a general practitioner are seen by emergency medicine residents and qualified EPs. Depending on the needs of the patient, the EP can consult the medical specialists. If a patient needs more specialised care or needs to be admitted to the ward, the necessary specialism is consulted and the patient is handed over to the specialist for further treatment. Referred patients are seen by (non) trainee residents of various medical specialities under the supervision of medical specialists belonging to the particular department.

St. Antonius Hospital is a large community medical centre with approximately 23,000 visits per year. There were seven trainee residents in emergency medicine working in shifts. Non-referred patients were seen by EP residents and supervised by qualified EPs and referred patients were seen by residents of a specific speciality supervised by the medical specialist. However, senior EPs were able to admit a patient for a specialism directly to the ward after a phone consultation with the specialist on call.

Selection of participants, data collection and processing

In the VUmc the study was conducted during a four-week period from 8 October until 4 November 2012. At St. Antonius Hospital, this was divided into two periods of two weeks each from 21 November until 5 December 2012, and from 11 February until 24 February 2013.

For all patients visiting the ED in these aforementioned weeks, the following time moments were registered: ED arrival, triage, first contact with a physician, and discharge from the ED, in addition to information on triage level, type of referral, ordering of radiological and diagnostic testing, discharge disposition, first and last consulting medical speciality and the total number of consultations. At VUmc, these data were extracted from paper forms filled in by nurses and physicians. At St. Antonius Hospital, data were retrieved from a computer system called Intracis.

In addition, data were collected by trained observers (medical students under the supervision of an internal medicine resident and a specialist) to obtain detailed information on different consecutive steps in the process of individual ED patient flow. The observers worked in shifts to cover all the days of the previously defined study periods, from 12.00-23.00 hours. For this additional follow-up, patients older than 18 and triaged to Emergency Severity Index (ESI) level 2 or 3 at VUmc, and Manchester Triage System (MTS) category orange or yellow at St. Antonius Hospital were selected.[4,5] This selection was based on the previous measurement, demonstrating that these categories had longer completion times.[3]

The additional data collection included time moments for the ordering, conduction and evaluation of radiological and diagnostic testing and the request, conduction and ending of a medical consultation. Also data on the time physicians arrived at their final diagnostic conclusions on the ED and when the nurses were informed that the patient could leave the ED were noted.

Outcome measures

The primary aim of this study is to measure the durations of the different diagnostic and therapeutic procedures that a patient is subjected to during their stay in the ED, and to evaluate which factors contribute to completion times longer than four hours. Secondly to compare whether there are differences in completion times between an academic centre run by ED physicians and also fellows and specialists from various departments and a large urban hospital run primarily by the EPs. And thirdly/finally to investigate whether the measures implemented after previous measurement at the VUmc have had a beneficial effect on completion times.

Primary data analysis

Data from the VUmc and St. Antonius Hospital were analysed separately. Exceeding a completion time of four hours was selected as the primary endpoint. Patients were split into two groups: patients with a completion time on the ED of less than four hours or a completion time of more than four hours.

For statistical analyses, two types of statistical tests were used. Pearson's chi-square test was used to assess the independence between the variable 'exceeding or not exceeding the four-hour target', and other variables including age category, triage level, and the number of consultations. The null hypothesis, which is an independence between the two variables, was rejected if the p-value was lower than 0.05 (significant dependency). The Mann-Whitney test, also called Wilcoxon or rank-sum test, was performed to compare the two populations of patients (exceeding and not exceeding the four-hour target) in terms of some duration variables. If the p-value was lower than 0.05, the null hypothesis that the distributions are similar was rejected, which means that the two distributions are significantly different and there is a significant dependency between exceeding / not exceeding the four-hour target and the chosen variable. The test allowed us to see whether the two populations had significantly different distributions of some durations such as door-to-doctor time and diagnostic tests for instance, and thus to know if there is a dependency between the two variables.

RESULTS

Characteristics of the study subjects

In the VUmc, 2272 patients were seen at the ED between 8 October and 4 November 2012, a total of four weeks. A subgroup of 372 ESI 2 and ESI 3 patients was followed closely by researchers to obtain more detailed information. In the St. Antonius Hospital there were 1656 patients of which a total of 492 orange- and yellow-triaged patients were closely observed for detailed information. The average age of patients in the VUmc was 40 years (SD 24.1); this was significantly higher in the St. Antonius Hospital with an average age of 50 years (SD 23.6), $p < 0.001$. Characteristics of all patients in both hospitals are summarised in *table 1*.

Time to completion

In the VUmc, 89% of the patients had a completion time of less than four hours. The average completion time

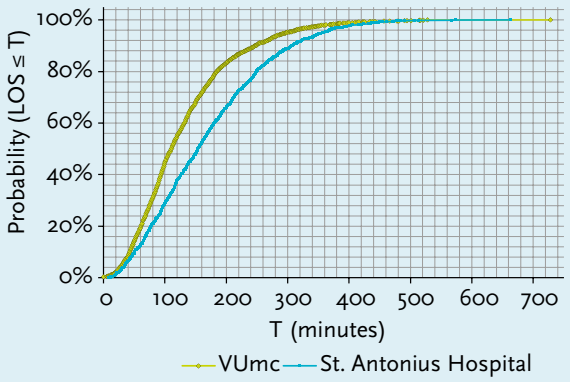
Table 1. *Patient characteristics*

	Site, no. (%)					
Variable	**VUmc (n = 2272)**			**St. Antonius Hospital (n = 1656)**		
Age	0-17 years	423	19%	0-17 years	183	11%
	18-64 years	1420	62%	18-64 years	923	56%
	65+ years	429	19%	65+ years	550	33%
Triage category	ESI 1	112	4.9%	Red	26	1.6%
	ESI 2	113	5%	Orange	346	21%
	ESI 3	1000	44%	Yellow	698	42%
	ESI 4	894	39.3%	Green	581	35%
	ESI 5	153	6.7%	Blue	5	0.3%
Arrival	Ambulance	531	23%	Ambulance	225	28%*
	Air ambulance	4	0.2%			
Discharge destination	Home	1737	76.5%	Home	1025	61.9%
	Hospital admission	535	23.5%	Hospital admission	631	38.1%

* Data only known for the patients on the ED between 11 February until 24 February 2013

(n = 2262) was 2:10 hours, (median 1:51 hours, range: 0:05-12:08). In the St. Antonius Hospital, 77% of patients had a completion time shorter than four hours (n = 1656). The average completion time in hours (n = 1655) was 2:49 (median 2:34, range: 0:08-11:04). *Figure 1* demonstrates the cumulative distribution of completion times for both hospitals.

Figure 1. *Cumulative distribution of completion time*



Triage

In the VUmc, most patients were categorised as ESI 3 (44%) and ESI 4 (39%) (*table 1*). A larger percentage of ESI 1, 2 and 3 patients did not achieve the four-hour target (14%, 20% and 19%) compared with ESI 4 and 5 patients (2.7% and 0%), $p < 0.001$.

At the St. Antonius Hospital, most patients were categorised as yellow (42%) and green (35%). A greater percentage of orange and yellow categorised patients exceeded the four-hour target (32% and 28%) compared with red (8%) and green/blue (13%), $p < 0.001$.

Number of specialities involved

In the VUmc, the average number of consultations per patient was 1.306, this was 1.155 in St. Antonius. For both hospitals there was a significant dependency between exceeding the four-hour target and whether a consultation was performed ($p < 0.001$). The realisation of the four-hour target was not linked to the number of consultations.

Age

In both hospitals, patients older than 65 years were more likely to stay in the ED for more than four hours ($p < 0.001$). *Figure 3* demonstrates the average completion time per age category.

Arrival pattern

Most patients arrived between 9.00 and 23.00 hours. An association was found for both VUmc ($p = 0.02$) and St. Antonius Hospital ($p = 0.02$) between arrival time and

Figure 2. *Number of consultations per hospital and the four-hour target*

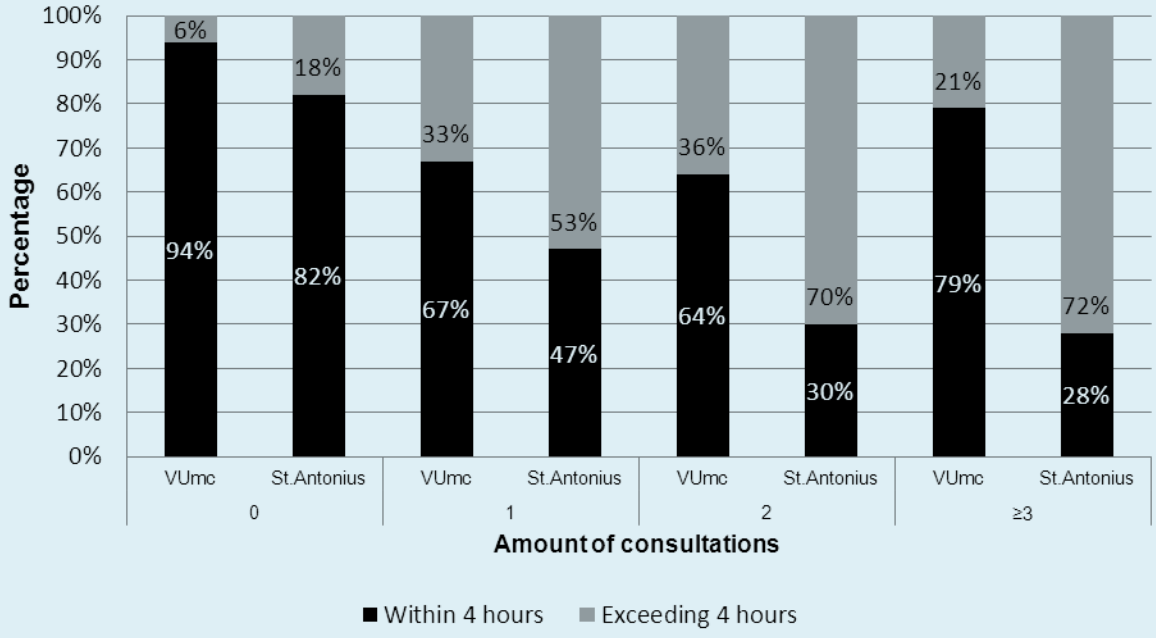


Figure 3. *Average completion time per age in both hospitals*

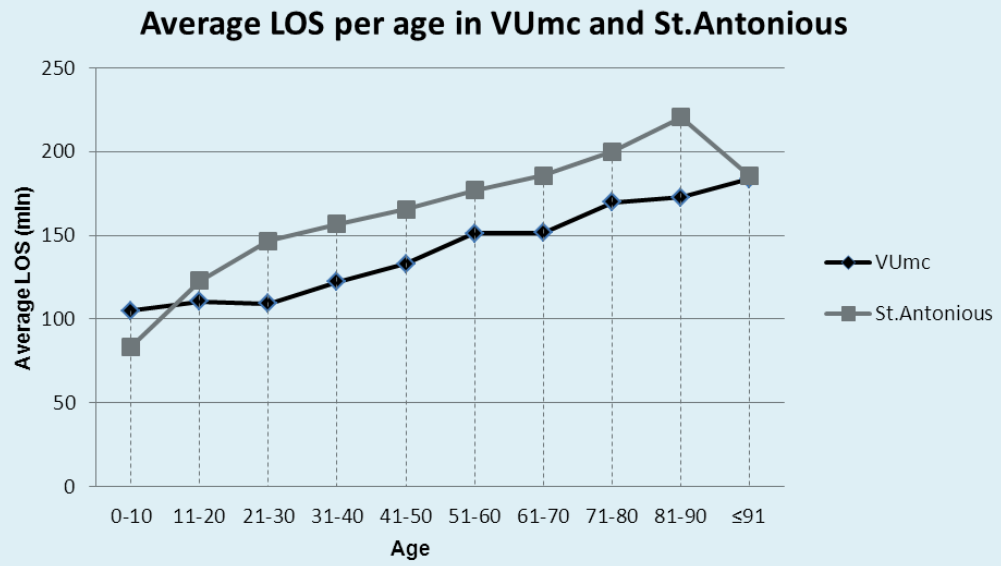
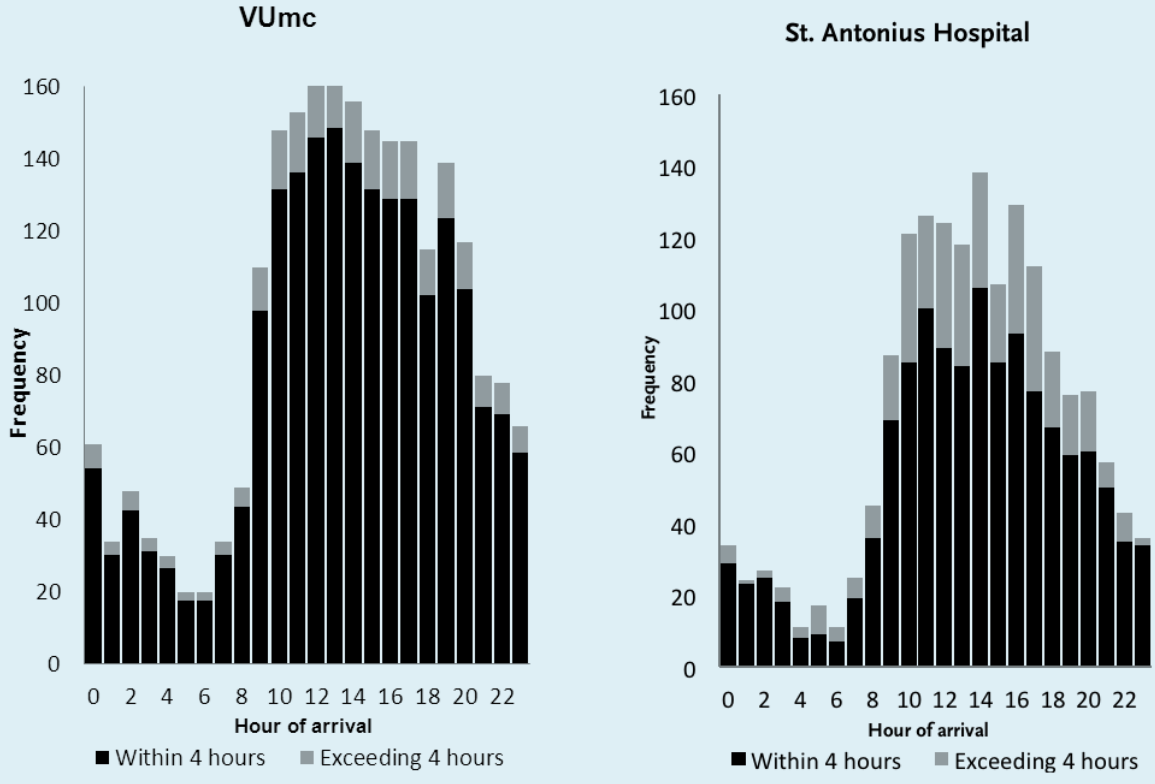


Figure 4. *Four-hour target and time of arrival*



the four-hour target (*figure 4*). No significant differences were found in exceeding the four-hour target between ED visits on different days of the week: VUmc (p = 0.054), St. Antonius Hospital (p = 0.16)

Door-to-doctor time

In the VUmc, the door-to-doctor time was not significantly different between patients who did or did not exceed the four-hour target, p = 0.07 (*figure 5*). In St. Antonius

Table 2. *Triage time and door to doctor time in all patients and in detailed patients*

	VUmc		St. Antonius	
All patients	**Minutes, N**	**Mean ± SE**	**Minutes, N**	**Mean ± SE**
Triage-time	7:11 N = 2204	1:12	12:08 N = 1656	00:19
Door to doctor time	27:08 N = 2258	00:34	37:20 N = 1655	00:54
Detailed patients	**Minutes, N**	**Mean ± SE**	**Minutes, N**	**Mean ± SE**
Triage time	6:12 N = 361	1:41	14:04 N = 494	00:46
Door to doctor	37:16 N = 371	01:51	39:44 N = 494	01:43

Hospital, there was a significant correlation for this analysis, $p < 0.001$ (*figure 5*).
The door-to-doctor times for all patients and for detailed measured patients are demonstrated in *table 2*.

Medical speciality

In the VUmc, most patients were seen by EPs and 4% of these patients exceeded the four-hour target. In 29% of the surgery patients, the four-hour target was exceeded, followed by neurology (27%) and internal medicine (24%). In the St. Antonius Hospital, most patients were seen by the EPs on behalf of different departments. The internal medicine department had the largest percentage of patients exceeding the four-hour target (40%) followed by lung diseases (35%) neurology (33%) and surgery (14%). In both hospitals a significant dependency was found between speciality and exceeding the four-hour target ($p < 0.001$).

Diagnostic tests

In the VUmc data of 283 detailed patients were useful for analysing diagnostic tests, as illustrated in *figure 6*. No significant difference in duration of 'prediagnostic tests' was found for patients who did or did not exceed the four-hour target ($p = 0.12$). For 'diagnostic tests' and 'time after diagnostic tests' there was a significant difference (both $p < 0.001$). In the St. Antonius Hospital there was a significant difference in the duration of all the sub-processes for patients (n = 349) who did or did not exceed the 4 hour-target.

Radiology

In the VUmc, 34% of patients underwent an X-ray, followed by CT scan (11.4%), ultrasound (8%) and MRI (0.4%). In the St. Antonius Hospital, 49% of patients underwent an X-ray, followed by CT scan (15%), ultrasound (7.9%) and MRI (0.4%). All radiology tests were correlated with a significantly higher chance to exceed the four-hour target. The patients in the VUmc who did not undergo any radiological tests had a chance of 4.9% of exceeding the four-hour target. This chance to exceed the target increased to 8.5% in patients only undergoing X-ray(s) ($p = 0.002$), and to 35.3% for patients only undergoing CT scan(s) ($p < 0.001$) and 33.3% for patients undergoing only ultrasound(s) ($p < 0.001$). In the St. Antonius Hospital the chance to exceed the four-hour target was 11% for those who did not have radiological tests. This chance increased to 22% for patients having only X-rays(s) ($p < 0.001$), to 49% for patients undergoing only CT scan(s) ($p < 0.001$) and to 45% for only undergoing ultrasound(s) ($p < 0.001$).
For both hospitals there was a significant correlation for the number of radiology tests and exceeding the four-hour target ($p < 0.001$), as shown in *figure 7*.

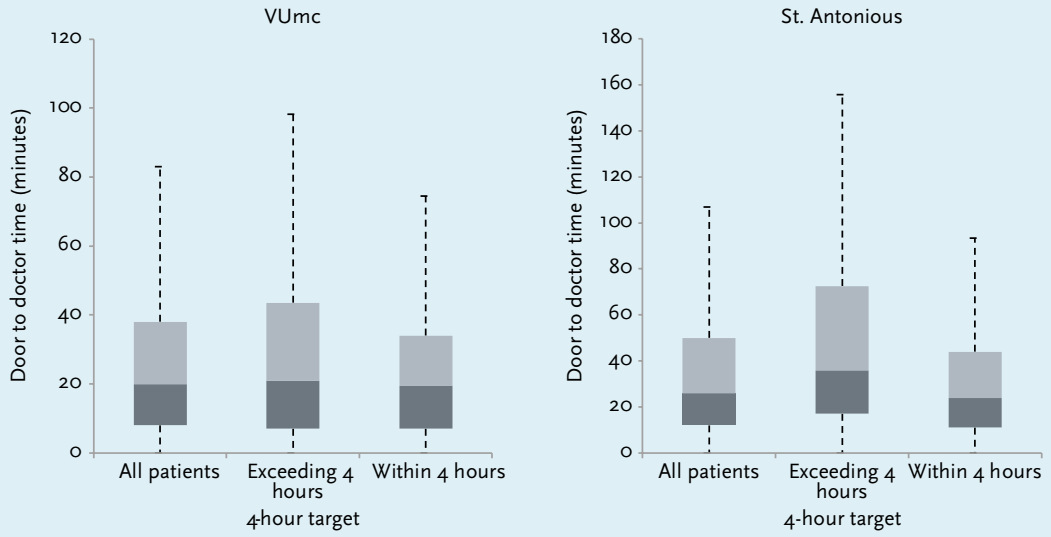
Discharge destination

In both hospitals, most ED visits did not result in a hospital admission (*table 1*). Patients who were admitted or transferred elsewhere were more likely to exceed the four-hour target in the VUmc (25% and 29% of exceeding) compared with those who were discharged (7%) ($p < 0.001$). In the St. Antonius Hospital 37.5% of admitted patients and 57.1% of transferred patients exceeded the four-hour target compared with 11.5% of released patients ($p < 0.001$).

VUmc 2010 compared with 2012

In February 2010, 84% of patients in the VUmc had a completion time of less than four hours and the average completion time was 2:23 hours (n = 2444). This was 89% in 2012 with an average completion time of 2:10 hours (n = 2262).
The average door-to-doctor time was 48 minutes in the subgroup of detail patients (n = 66) in the study of 2010. This was 37 minutes in the subgroup of 371 detail patients in this study in 2012.

Figure 5. *Door-to-doctor time in minutes and the four-hour target*



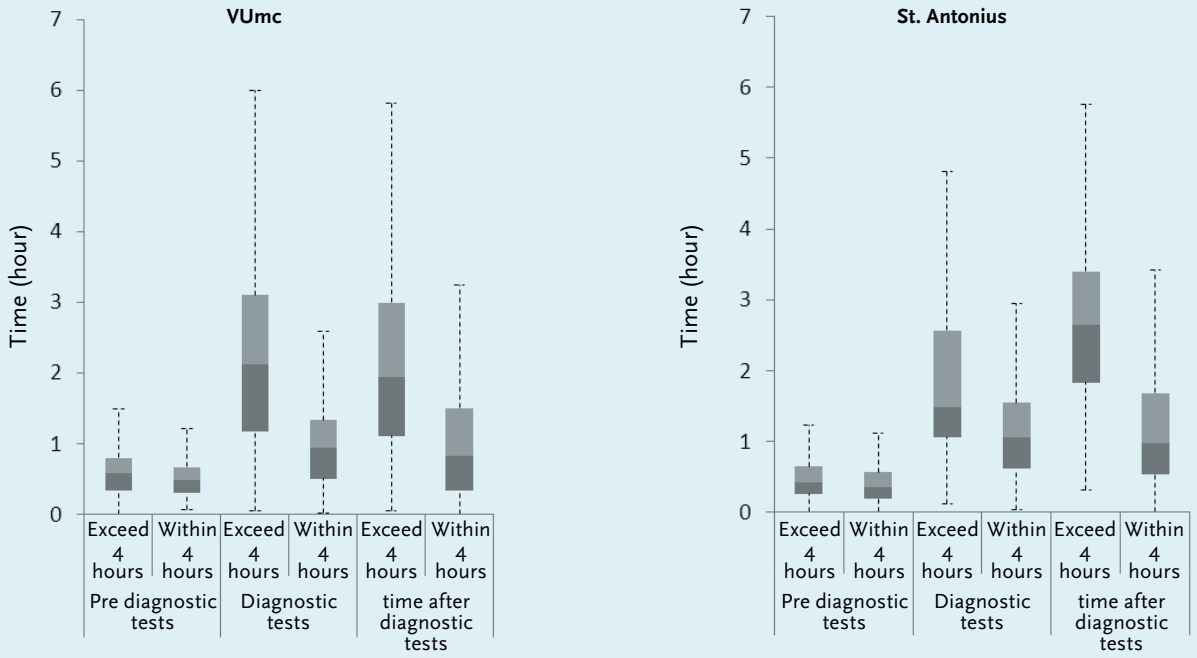
In the previous study and in this study, no association was found in the VUmc between the arrival time of a patient and the four-hour target. The previous study in the VUmc demonstrated that internal medicine had most patients exceeding the four-hour target (37%), followed by neurology (29%) and surgery (28%). In this study, internal medicine accounted for 24% of the cases exceeding the four-hour target. In both studies, 39% of patients were triaged as ESI 3. In 2010, 24% of these patients did not achieve the four-hour target, this was 19% in 2012. In both studies the absolute number of patients exceeding the four-hour target, were ESI 3 patients. In 2010 and 2012 for both sub-process 'diagnostic tests' and 'time after diagnostic test' there was a significant difference in durations of patients who do and do not exceed the four-hour target.

DISCUSSION

In this study we found that patients older than 65 years, patients seen by more than one specialism and patients undergoing radiological tests are more likely to have longer completion times in both hospitals. We aimed to detect factors contributing to a longer stay on the ED in two hospitals with different work procedures and different patient populations. In the VUmc a higher percentage of ESI 1 patients were seen compared with the number of red-triaged patients in the St. Antonius Hospital, due to the fact that the VUmc is a level 1 trauma centre. However, more orange-triaged patients were seen in the St. Antonius Hospital compared with ESI 2 patients in the VUmc, probably because acute cardiology patients (mostly ESI 2) are not presented to the ED in the VUmc but to the cardiology department. Notably, more older patients were seen in the St. Antonius Hospital. In the VUmc, non-referred patients were seen by EP trainees who were supervised by a qualified EP. If the expertise of a specific speciality was needed, a resident of this speciality was consulted and supervised by the medical specialist. Referred patients were directly seen by the residents of a specific speciality and supervised by the medical specialist. In the St. Antonius Hospital, non-referred patients were mostly seen by EP residents and referred patients were mostly seen by residents from the speciality. However, in St. Antonius Hospital senior EPs were able to independently discharge or admit a patient for a specific speciality after a phone consultation with a medical specialist of the department. Probably as a result of this difference in work procedure, more consultations were performed in the VUmc.

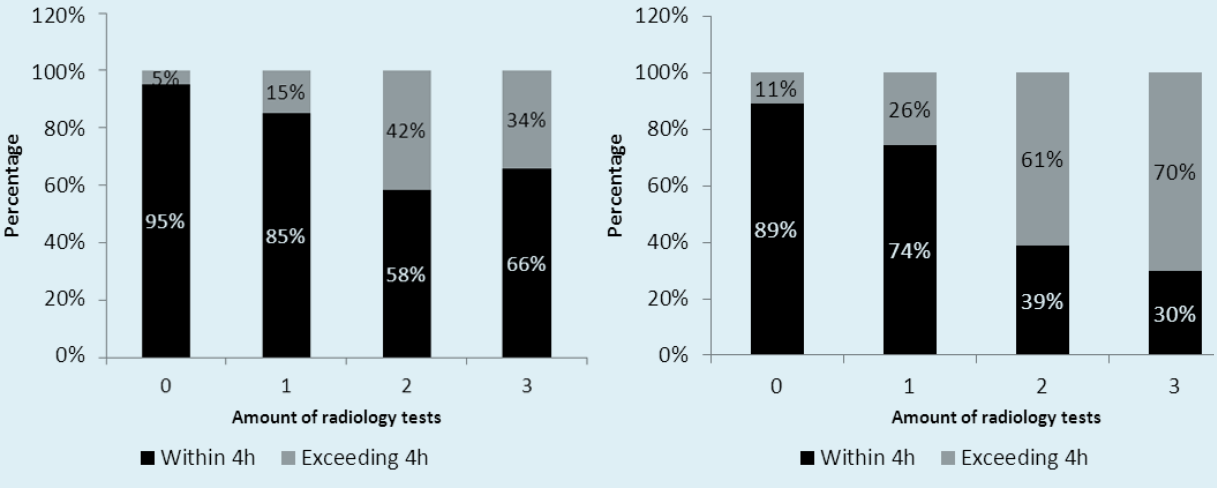
Despite these differences, both hospitals were facing largely the same problems. Factors increasing the chance of exceeding the four-hour target were: older age, having at least one consultation and undergoing radiological testing. These patients were predominantly found in the higher triage categories. However, in the most acute category (ESI 1 or category red), patients are treated in the shock room by a team of specialists directly after arrival on the ED with the opportunity to perform radiological testing at the bedside, resulting in a relatively short completion time on the ED. Patients in triage categories ESI 2/3 and orange/yellow, however, are not initially seen by a team of specialists despite the fact that this group of patients is also relatively old and frequently have multiple comorbidities demanding the expertise of more than one specialist.

Fig 6. *Boxplots of the durations of sub-processes prediagnostic tests, diagnostic tests and time after diagnostic tests for patients who did or did not exceed the four-hour target*



Consultations occurred consecutively in these patients contributing to a longer completion time in both hospitals. Brick *et al*. also concluded that multiple consultations and advanced age were significantly associated with a longer stay on the ED.[6] Consulting physicians tend to treat the patient individually, one after the other, instead of working as a team. This fragmented delivery of care increases the length of stay and may thereby lead to complications and reduced patient satisfaction. A proposed solution for this problem in our previous study was the introduction of assessment teams for these patients. Especially in old patients with multiple comorbidities it was decided that specialities such as internal medicine, neurology, surgery or emergency physicians should be called upon to examine the patients together as a team at the outset so that multiple, consecutive consultations could be avoided. However, although we have propagated this concept intensively in the last few months the doctors still seem to

Fig 7. *Realisation of the four-hour target and the amount of radiology tests*



follow the traditional method of examining/treating these patients consecutively one after the other.

In 2010, the completion times were measured in the VUmc in order to explore the delaying factors contributing to stagnation on the ED. After the results were known, new measures were implemented to improve the patient flow. The most important measure was that the supervising internist stayed in the hospital until 23.00 hrs. instead of 18.00 hrs. In addition the shifts covered by qualified EPs were adjusted. During weekdays the shifts were extended from 08.00-17.00 hrs to 08.00-23.00 hrs and in the weekend they were available for supervision by phone. Two years later we noticed some improvements, the completion time within four hours increased from 84% in 2010 to 89% in this study. The internal medicine department showed the largest decrease in patients exceeding the four-hour target, from 37% to 24%. This is probably due to the increased working hours of the supervising internist, which probably quickens the decision-making process. Bucheli also demonstrated that adding a second physician during the evening shifts of the internal medicine department significantly reduced the time spent on the ED.[7] In addition the change in the mindset of the residents and specialists of the internal medicine department after the publication of the first results might have improved the working efficiency on the ED of this specialism

Despite booking the above-mentioned improvements compared with 2010, we do experience some of the same problems in the VUmc. We still see patients stay relatively long on the ED after all the diagnostic tests are finished. After interviewing some of the nurses and residents, it was proposed that the main cause for this delay was the lack of direct supervision on the ED. Residents often see patients alone on the ED and telephone their supervisor after finishing anamnesis, physical examination and first diagnostic tests. They tend to collect patients and/or problems before they call their supervisor, especially during late hours when the senior specialist is no longer in the hospital. In addition, during the daytime supervisors are not always directly available to discuss a case on the phone with the resident, because they are also busy supervising on the wards or the operating room.

Furthermore, the use of diagnostic procedures such as CT scans has increased in the last decade, as they improve diagnostics and therapeutic decision-making, but on the other hand they also take up a long completion time.[8,9] In this study, all radiological tests were correlated with a longer completion time on the ED, and CT scan especially. It is known that it takes time before all the images of the CT scan are uploaded and available for the radiologist to interpret. In our opinion more emphasis should be placed on timely performance and interpretation of radiology testing in the ED setting.

Even though ED crowding and long completion times are an intensely debated issue and a serious problem in many countries, the Netherlands together with some other Scandinavian countries seem to perform relatively well in delivering timely patient care at the ED.[10] This may also be due to a strong network of patient care outside the ED, such as the prehospital and primary care that is also available after-hours, which makes it easy for the clinicians to discuss the case with GPs and take necessary measures together. However, the patients who do stay longer in our hospital are old and vulnerable, which increases the risk of complications in this group. As shown in an earlier study these patients are known to have about three comorbidities and used an average of 5.3 different medications.[11] Therefore, in our opinion these results should be taken seriously and remedial measures such as introduction of assessment teams, improving the direct supervision of the resident to speed up the process of decision-making, and increasing the radiological support in the ED should be introduced in the EDs.

This study was performed in two large hospitals with a large number of inclusions which makes the conclusions generalisable to the situation in the Netherlands.

STUDY LIMITATIONS

Firstly, in this study detailed information was only obtained by the researchers for ESI 2/3 and orange/yellow categorised patients. We chose to closely observe this group because earlier research pointed out that this group had, in absolute numbers, the longest completion time on the ED. Selection of these patients might underexpose logistic problems occurring in the other triage categories. However, as the completion time in these triage categories was significantly lower we presume the impact of this selection on the overall results was minimal. Secondly, the triage systems of hospitals were different, which can introduce bias. However, in the Netherlands both triage systems are frequently used and are largely comparable in determining the severity of the condition of the patient.

Thirdly, the measuring period was not at the same time in the two hospitals. Seasonal influence may alter the situation. However, the benefit of measuring in both hospitals one after another is that we had the same team of researchers, using the same technique during both study periods. Finally the researchers were physically present on the ED floor to note every step in the process of the selected patients. This might alter the attitude of the treating physician/nurses, and speed up or slow down the normal routine of the physicians and nurses on the ED.

CONCLUSION

In this study performed on the EDs of two different hospitals with different working strategies and patient populations, we see that the factors leading to ED stagnation were similar, namely: old age of the patients, treatment by more than one speciality and undergoing radiological tests. Compared with the measurements in 2009 for the internal medicine department, we do see some improvements in the VUmc during this study. This department extended the hours in which the supervising specialist was in the hospital after the study results in 2009. This more direct contact between supervisors and residents might help to quicken the process of decision-making, after all diagnostic tests are performed. Despite this small improvement, still the same vulnerable group of patients has the longest completion time on the ED. We noticed that it is difficult to make substantial changes in the workflow of an emergency department. We still think that uniform remedial measures should be taken nationwide to deal with these factors to reduce stagnation in the EDs.

DISCLOSURES

The authors declare no conflicts of interest.

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CASE REPORT

Thinking beyond the mass: ANCA-associated vasculitis mimicking a pancreatic malignancy

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ABSTRACT

Isolated pancreatic involvement is a rare initial presentation in patients with ANCA-associated vasculitis. We report a patient with a suspected malignant pancreatic mass, referred to our hospital for pancreaticoduodenectomy. However, the pancreatic mass proved to be the initial manifestation of ANCA-associated vasculitis.

KEYWORDS

ANCA-associated vasculitis, pancreatic mass, pancreatitis, malignancy

What was known on this topic?
ANCA-associated vasculitis (AAV) predominantly affects the kidneys and the respiratory tract. Involvement of the extra-renal visceral abdominal organs is rare and has only occasionally been described as the initial manifestation of AAV.

What does this case add?
The initial manifestation of AAV as a pancreatic mass or pancreatitis is very rare. A complete medical history to detect constitutional symptoms and knowledge about atypical presentations of AAV can accelerate the diagnostic evaluation and prevent severe AAV-related morbidity and unnecessary pancreatic resection.

INTRODUCTION

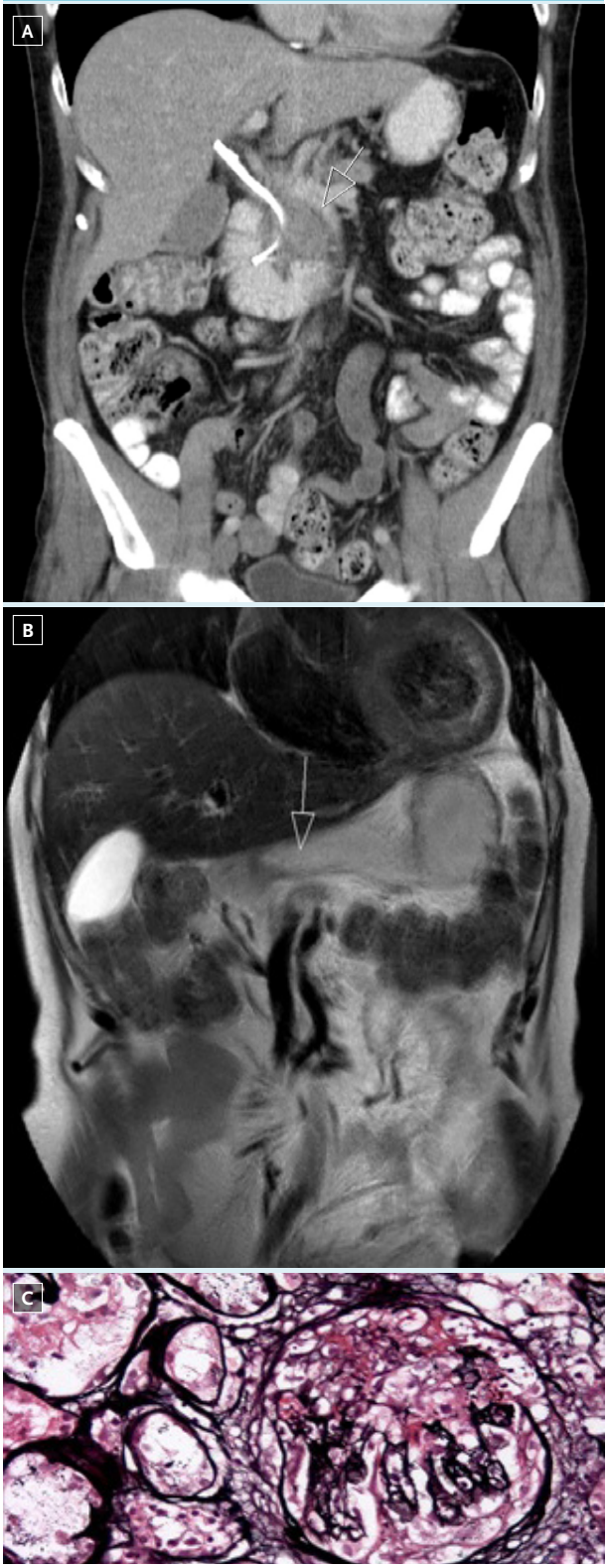
Pancreatic surgery offers the only chance of a cure in patients with localised pancreatic cancer. There is general consensus that pathological confirmation is not mandatory before proceeding to pancreatic surgery in patients with a mass clinically and radiologically suspected of pancreatic malignancy. The downside of this approach is that 5-13% of the suspected pancreatic malignancies appear to be a benign disease,[1,2] mostly chronic pancreatitis. In this case report we describe a patient in whom a pancreatic mass suspected of malignancy proved to be the initial presentation of ANCA-associated vasculitis (AAV).

CASE REPORT

A 57-year-old man was referred to our hospital for pancreatic surgery, because of a pancreatic mass that was highly suspicious of malignancy. Four weeks before, he was admitted to another hospital with fatigue, severe weight loss and painless jaundice. Physical examination was normal, except for signs of jaundice. Laboratory results showed cholestatic jaundice and slightly elevated alanine and aspartate aminotransferases (92 and 58 U/l, respectively). The amylase level and renal function were normal. Endoscopic retrograde cholangiopancreatography showed a stenosis of the distal common bile duct. Endoscopic papillotomy was performed with placement of a biliary stent at the level of the stenosis. Cytological examination showed atypical cells but no malignant cells. An abdominal computed tomography scan (CT) revealed a 25 mm soft tissue mass at the medial site of the stent without distant metastases (*figure 1a*). After these diagnostic and therapeutic procedures the patient was discharged out of the hospital and referred for pancreatic surgery to our hospital.

At presentation in our hospital, two weeks later, the patient reported multiple episodes of epistaxis in the past two

Figure I. *Computed tomography at first presentation: a 25 mm mass with solid characteristics at the medial site of the biliary stent (a), MRI (4 months after CT): normal pancreas without pancreatic duct dilatation or a pancreatic mass (b), renal histology with pauci-immune necrotising crescentic glomerulonephritis (40x, Jones silver stains) (c)*



weeks and oliguria for two days. Physical examination showed nasal crustae, conjunctivitis of both eyes, tenderness in the epigastric region and pitting oedema of both ankles. Laboratory results showed normalisation of bilirubin and transaminases, but now severe renal failure (creatinine level 1031 µmol/l). Additional investigations revealed 1+ proteinuria and haematuria. ANCA was positive with a perinuclear pattern and specificity for myeloperoxidase (MPO-ANCA). Chest X-ray was normal and neither abdominal MRI nor endo-echography with cytological examination showed evidence of a pancreatic mass or malignancy. A renal biopsy showed a pauci-immune necrotising crescentic glomerulonephritis of > 50% of the glomeruli with negative immunofluorescence for IgG, IgA, IgM, fibrinogen, albumin, C3, kappa and lambda (*figure 1c*). Biopsy of the nasal crustae showed chronic and superficial ulcerative inflammation, without the specific characteristics of AAV, such as vasculitis, necrosis or granulomatosis.

The diagnosis ANCA-associated vasculitis (AAV) with pancreatic, nasal, conjunctival and renal involvement was established. The patient was treated with corticosteroids, oral cyclophosphamide and plasmapheresis. With this treatment, the conjunctivitis, epistaxis and fatigue resolved, but renal function did not recover. Abdominal MRI was repeated after four months of treatment and showed no signs of pancreatic cancer (*figure 1b*). Six months after starting haemodialysis the treatment was converted to peritoneal dialysis.

DISCUSSION

AAV is a group of multisystem diseases, which are characterised by necrotising vasculitis. The ANCA-associated vasculitides include granulomatosis with polyangiitis, microscopic polyangiitis, Churg-Strauss syndrome and renal-limited vasculitis. AAV has an annual incidence of 12-20 per million with a higher prevalence in older adults (> 50 years) and Caucasians.[3,4]

AAV predominantly affects the kidneys and lungs with eye, ear, nose or throat involvement often present at diagnosis. The initial presentation of AAV with pancreatic involvement has been described in a few case reports (*table 1*).[5-13] These reports show that pancreatic involvement can either manifest as acute pancreatitis or as a pancreatic mass.[5-13] In patients who presented with acute pancreatitis, the diagnosis of AAV was only established when additional, more typical, symptoms of AAV such as renal involvement manifested.

In most patients who presented with a pancreatic mass, the diagnosis of AAV was established after surgery.[7,12,13] Knowledge that a pancreatic mass can be a manifestation of AAV or (IgG4-related) autoimmune pancreatitis (AIP)

Table 1. *Summary of reported cases of ANCA-associated vasculitis presenting as acute pancreatitis*

Presentation	Age	Interval between pancreatic disease and diagnosis of AAV	Diagnostic criteria	Outcome	Reference
Acute pancreatitis	47 years	2 months	PR3-ANCA Nasal biopsy	Improved on cyclophosphamide and steroids	8
Acute pancreatitis	20 years	1.5 months	PR3-ANCA Renal biopsy	Died due to complications of AAV	5
Acute pancreatitis	65 years	1 month	PR3-ANCA Autopsy	Died due to complications of AAV	9
Acute pancreatitis	45 years	Unknown	ANCA negative Parotid biopsy: necrotising vasculitis with granulomas	Improved on cyclophosphamide and steroids	11
Acute pancreatitis	60 years	2 months	PR3-ANCA Renal biopsy	Improved on cyclophosphamide and steroids	6
Pancreatic mass	62 years	During hospitalisation	ANCA Renal biopsy	Improved on cyclophosphamide and steroids	10
Pancreatic mass	50 years	Postoperative	PR3-ANCA Pancreatic histopathology: granulomatous vasculitis	Improved on cyclophosphamide and steroids	7
Pancreatic mass	48 years	Postoperative	ANCA negative Pancreatic histopathology: necrotising vasculitis with granulomas	Improved on cyclophosphamide and steroids	12
Pancreatic mass	62 years	Postoperative	PR3-ANCA Pancreatic histopathology: necrotising vasculitis with granulomas	Improved on azathioprine and steroids	13
Pancreatic mass	57 years	Preoperative	MPO-ANCA Renal biopsy	Improved on cyclophosphamide and steroids	Present case

ANCA = anti-neutrophil cytoplasmatic antibodies; MPO-ANCA = ANCA directed against myeloperoxidase; PR3-ANCA = ANCA directed against proteinase 3.

can prevent unnecessary surgery. In addition, the presence of atypical symptoms and multi-organ involvement in patients presenting with a pancreatic mass should raise suspicion of other diagnoses than malignancy. Rapid recognition of AAV is important as early treatment of AAV results in a greater likelihood of complete or partial reversibility of the disease.[14] Imaging characteristics of the pancreatic mass on CT scan and MRI scan can be helpful to differentiate between AAV or AIP and pancreatic cancer. Serological markers such as IgG4, ANCA and CA-19-9 are inconclusive.[9,15] Imaging characteristics such as decreased enhancement in the pancreatic and hepatic phase on CT and a lesion with upstream dilatation of the main pancreatic duct with high diffusion coefficient on MRI are signs that make pancreatic cancer more likely.[15]

In our patient unnecessary surgery was prevented, but despite immediate immunosuppressive treatment the patient remained dialysis-dependent. This corresponds with the observation in other case reports that pancreatic involvement in patients with AAV seems to be related to a more rapid progressive course of disease, with even two fatal outcomes.

CONCLUSION

Our case demonstrates that a pancreatic mass can be a first presentation of AAV. Awareness that pancreatic manifestations may be part of AAV is important for the timely diagnosis and treatment of AAV. This may prevent severe morbidity and unnecessary surgery.

DISCLOSURES

The authors declare no conflicts of interest.

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CASE REPORT

Clozapine intoxication due to cessation of smoking and infection

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ABSTRACT

We report on a patient on clozapine treatment who was admitted to our hospital with pneumonia. He had stopped smoking a few weeks before admission. The serum clozapine rose to a toxic level, most likely due to the combination of infection and smoking cessation. Physicians and pharmacists are often not aware of risk factors for decreased metabolism of clozapine.

KEYWORDS

Clozapine, CYP1A2, infection, inflammation, smoking

What was known on this topic?
Polyaromatic hydrocarbons in cigarette smoke induce the CYP1A2 enzyme. Infection and/or inflammation can inhibit CYP1A2. Both cessation of smoking and infection may increase clozapine serum levels.

What does this add?
In psychiatry, healthcare professionals are well aware of the risk of cessation of smoking and/or infection in patients using clozapine. Dose reduction, preferentially guided by therapeutic drug monitoring, is the measure of choice when these risk factors are identified. In somatic settings, physicians and pharmacists are less aware of these risk factors because the psychiatric disease is often not the primary point of care. Admission to a hospital with an infection may lead to a necessary cessation of smoking, so at that moment patients using clozapine are at risk of toxic levels. This case report helps physicians and pharmacists to recognise and manage these risk factors earlier.

INTRODUCTION

Clozapine is an atypical antipsychotic used in the treatment of therapy-resistant schizophrenia. Its use is limited by rare occasions of agranulocytosis, necessitating frequent monitoring of blood cells. Despite this burden, clozapine use is increasing because it is often the only remaining option in therapy-resistant schizophrenia. We report on a patient on clozapine treatment, who was admitted to a general hospital with pneumonia and who had recently stopped smoking.

CASE REPORT

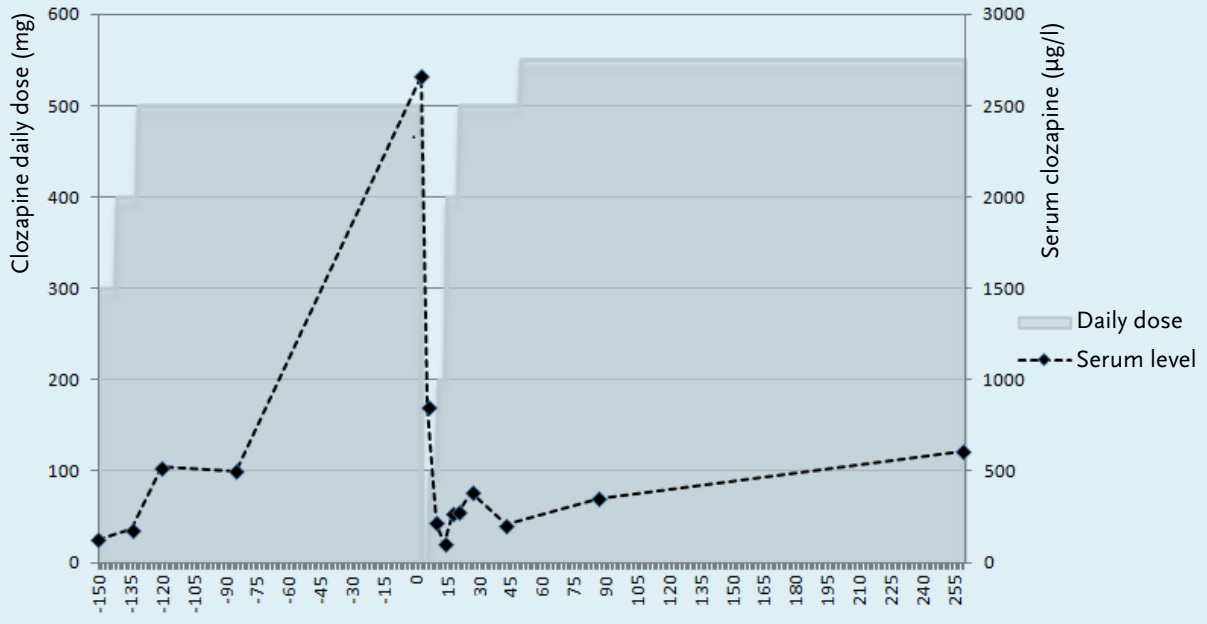
A 50-year-old man, suffering from schizophrenia and type 2 diabetes, living in sheltered housing, had been on clozapine treatment for 18 months. Before hospital admission, he had been on a stable dose of 500 mg daily for several months with a plasma level of clozapine of 502 µg/l, which is well within the therapeutic range of 350-700 µg/l (desmethylclozapine 295 µg/l). He had irregular smoking habits, up to 40 cigarettes a day in his smoking periods. A few weeks before admission he had ceased smoking. His daily medication included paroxetine, simvastatin, metformin, gliclazide, lorazepam and hydrocortisone/miconazole ointment. He presented to the emergency department with dyspnoea, chest pain and cough. There was no fever, but the laboratory parameters showed a leucocyte count of 32.9 x 10^9/l and a C-reactive protein of 256 mg/l. Chest X-ray showed empyema in the right chest. Because of respiratory insufficiency, he was admitted to the intensive care unit (ICU), intubated and sedated for 11 days. Empiric antibiotic therapy was started with ceftriaxone and erythromycin. The empyema

was treated by video-assisted thoracoscopy, drainage and rinsing with normal saline and streptokinase solution.
Medication in the ICU included midazolam, morphine, nadroparin, paracetamol, esomeprazole, phenylephrine, insulin, furosemide, and aerosolised fenoterol and ipratropium. Clozapine was continued on a daily dose of 500 mg.
During routine medication review, it was realised that there were risk factors for inhibited metabolism of clozapine. On day 4, the clozapine serum levels were strongly elevated: clozapine 2663 µg/l and desmethylclozapine 761 µg/l. Toxic side effects of clozapine were not seen, but symptoms such as seizures, somnolence, hypotension, dysarthria, ataxia, balance disorders and sialorrhoea might have gone unnoticed due to sedation. Clozapine treatment was stopped immediately.[1]
On day 7, the clozapine and desmethylclozapine levels had decreased to 848 and 405 µg/l, respectively. The calculated elimination half-life of clozapine in our patient was 39 hours, compared with a normal half-life time of approximately 14 hours. On day 8, clozapine was restarted at a lower dose of 100 mg a day, and over the next 14 days increased stepwise to the original dose of 500 mg daily. Initially, serum levels decreased to 103 µg/l, and thereafter increased to 386 µg/l. A graphical display of the daily dose of clozapine and serum levels is presented in *figure 1*.
On day 15, a tracheostoma was placed and weaning of ventilation was started. During the four days after reduction and cessation of the sedation, the patient experienced schizophrenic symptoms, particularly acoustic hallucinations. Although not measured on a daily basis, the clozapine serum levels were probably still subtherapeutic at this stage.
One month after admission, the patient was discharged to his sheltered home. His schizophrenia was stable with a daily clozapine dose of 550 mg and clozapine plasma levels of 353 µg/l at eight weeks after discharge and 611 µg/l at 32 weeks after discharge.

DISCUSSION

Our patient had been on a stable clozapine intake for a prolonged period, with a therapeutic clozapine level three months before admission. Upon admission to the hospital, two inhibiting mechanisms on clozapine metabolism worked simultaneously: cessation of smoking and inflammation.
Clozapine is mainly metabolised by cytochrome P-450 enzyme system (CYP), particularly CYP1A2. Other enzymes such as CYP2C19, CYP3A4, CYP2D6 and UGT 1A3/4 play a minor role in the metabolic pathway.[1,2] Polyaromatic hydrocarbons in cigarette smoke are the cause of CYP1A2 induction.[3] A study conducted by Faber *et al.* showed a rapid decrease in CYP1A2 activity after cessation of heavy smoking, starting a few days after smoking, with an apparent half-life of CYP1A2 activity decrease of 38.6 hours. After seven days of smoking cessation the decrease in CYP1A2 activity is at its maximum,[4] leading to a new clozapine plasma steady state

Figure 1. *Clozapine daily dose and serum levels, before, during and after admission*



Ten Bokum et al. Clozapine intoxication due to cessation of smoking and infection.

level after approximately seven days. In a study performed by Murayama-Sung *et al.* the average rise in clozapine plasma levels after smoking cessation was 46% (range -9.8% to +244.4%).[5]

There is evidence that the inducibility of CYP1A2 is dependent on gene polymorphism, with carriers of CYP1A2*1F (-163C>A, rs762551) polymorphism showing an increased inducibility.[6,7] Patients with this gene polymorphism have a higher risk of toxic clozapine levels when CYP1A2 induction diminishes after smoking cessation.

Infection and/or inflammation can also inhibit CYP1A2; activity may be reduced by up to 90% because of increases of interleukin-6, interferon and tumour necrosis factor-alpha during acute infectious and/or inflammatory processes.[8,9] Clozapine serum levels may increase by a factor 2 to 3.[9,10]

Separately, the effects of cessation of smoking and inflammation have been documented in the literature, but little is known about the extent of the rise of clozapine serum levels due to the combination of cessation of smoking and infection. The combination of both inhibiting effects resulted in a fivefold increase of clozapine serum levels in this patient. However, it is difficult to unravel the extent of the individual effects of smoking cessation and severe infection on clozapine levels.

Other drugs that are CYP1A2 substrates, such as caffeine, fluvoxamine, olanzapine and theophylline, can also be affected by smoking.[11] Decreased theophylline clearance has been described in respiratory infections and pneumonia.[12]

About 62% of all schizophrenic patients are active smokers.[13] Cessation of smoking is thus a frequent issue that arises with clozapine treatment. Healthcare workers in psychiatric healthcare institutions are well acquainted with the phenomena of altered clozapine metabolism at the start or cessation of smoking or with infections, and clozapine dosing is frequently adjusted and clozapine serum levels are frequently monitored.

In somatic healthcare institutions, psychiatric medication is often not the primary focus of care. However, most patients are forced to stop smoking as soon as they are hospitalised. Also infections are a common cause of hospitalisation. Thus, clozapine users who are hospitalised combine these risk factors for toxic clozapine levels. Toxic effects might not be recognised in time due to intubation, artificial ventilation and sedation. There is no antidote for clozapine; in case of severe toxicity, treatment should consist of supportive measures.[1]

When schizophrenic patients are admitted to somatic hospitals, there is often a strong inclination to continue antipsychotics, especially when psychiatric symptoms are severe. In retrospect, earlier anticipation could have avoided the toxic clozapine levels in our patient. In addition, decision support systems managed by a clinical pharmacist could have been helpful, by identifying all newly hospitalised clozapine users. Dose reduction, preferentially guided by therapeutic drug monitoring, is the measure of choice when risk factors are identified.

CONCLUSION

Risk factors for toxic clozapine levels due to infection and smoking cessation are often not recognised in somatic settings. Physicians and pharmacists should be aware of these risk factors and should be prepared to manage them adequately.

DISCLOSURES

The authors declare no conflicts of interest.

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PHOTO QUIZ

A potentially hazardous object with benign appearance at the outset

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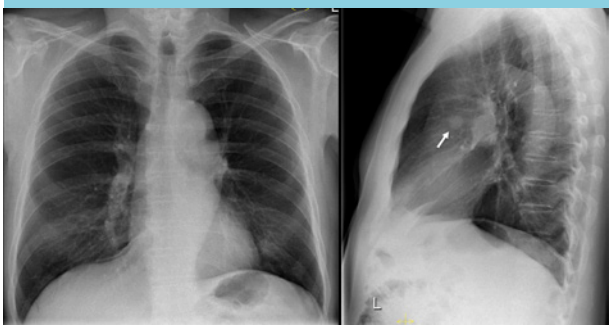
CASE REPORT

We present the case of a 73-year-old male patient who was referred to our outpatient department because of a solitary pulmonary nodule on routine chest X-ray (*figure 1*). His medical history comprised mood disorders, benign prostatic hyperplasia, adequately treated hypertension and asbestos exposure. He had never been hospitalised previously and a chest X-ray was requested as part of the routine work-up by the neurologist for mild cognitive impairment. The patient was free of pulmonary symptoms. Physical examination and biochemical and haematological tests revealed no relevant findings. Lateral chest X-ray revealed a discrete, homogenous round nodule with smooth borders, projecting over the ascending aorta, which was not visible on the posteroanterior view (*figure 1*).

Figure 1. *Lateral chest X-ray showing a homogenous round nodule (arrow), projecting over the ascending aorta, which is not visible on the posteroanterior view*



WHAT IS YOUR DIAGNOSIS??

See page 349 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 348)

A POTENTIALLY HAZARDOUS OBJECT WITH BENIGN APPEARANCE AT THE OUTSET

DIAGNOSIS

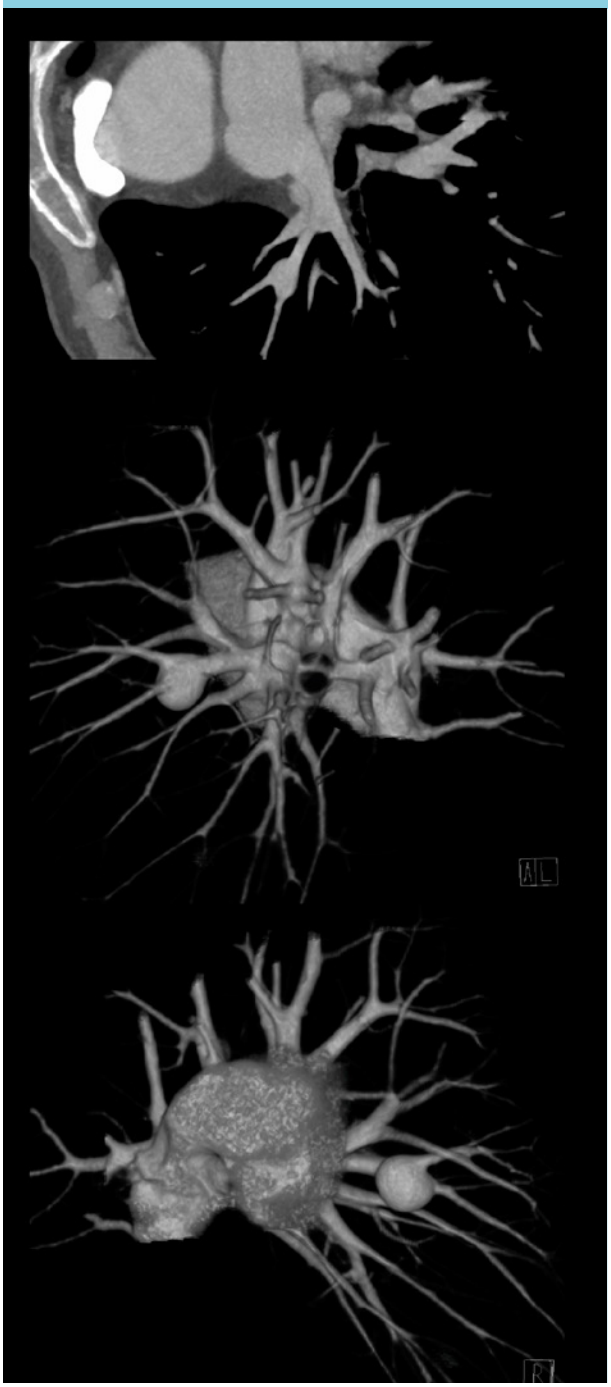
A solitary pulmonary nodule is a frequent incidental finding on routine chest X-rays. The majority of these nodules – especially in the young and non-smoking population – represent a benign (non-cancerous) lesion with a broad differential diagnosis. Since a malignant process is the most important cause to exclude, additional imaging is warranted. In some cases, additional imaging creates a new therapeutic dilemma.

In the present case, computed tomography (CT) scan revealed a bifurcation aneurysm of the left pulmonary artery at the level of the superior lingular segment of the left upper lobe, with a maximum diameter of 15 mm (*figure 2*). Digital subtraction angiography corroborated these findings, pulmonary artery pressure during this procedure was within normal limits (27/8 mmHg). Patient history, physical and diagnostic examination did not reveal any clues for underlying congenital or acquired conditions that might act as causal mechanism.

Idiopathic pulmonary artery aneurysms (PAA) are extremely rare, and the majority are located in the main pulmonary artery.[1,2] Patients are either asymptomatic, or their symptoms are not specific and resemble those of common cardiopulmonary conditions. Hence, the danger lies in acute dissection or rupture of the PAA, which will almost certainly lead to sudden death by aspiration and asphyxia after intrapulmonary haemorrhage.[3] Since the low prevalence of PAA and the fact that symptoms in the acute setting of rupture may also be limited to dyspnoea and chest pain, patients might initially be easily misdiagnosed as a pulmonary embolism or acute coronary syndrome. Subsequent mismanagement with antithrombotic agents might further enhance the risk of haemorrhage.[4]

The risk to develop a dissection or rupture depends on the actual size of the aneurysm or rate of progression of PAA diameter, and early diagnosis and treatment are crucial for this reason. However, due to the low prevalence of PAA and the diversity of causative factors, no standardised clinical management and treatment guidelines are available. Reported therapeutic options comprise angiographic embolisation or selective exclusion of the aneurysm by means of a covered stent in specific cases, video assisted thoracoscopic (VATS) lobectomy, or active surveillance by means of (annual or bi-annual) CT imaging for smaller aneurysms. Surgical intervention is preferred since it is curative and importantly may also be diagnostic. In order to choose between active surveillance and surgical intervention, there is no clear consensus regarding an adequate cut-off in diameter of the aneurysm, but an aneurysm more than double the size of the normal diameter of the affected vessel has been proposed.

Figure 2. *Volume rendered reconstruction CT scan showing the aneurysm of the left pulmonary artery at the level of the superior lingular segment of the left upper lobe, with a maximum diameter of 15 mm*



The patient was discussed in a multicentre and multidisciplinary team. Angiographic embolisation

of the aneurysm or selective exclusion by means of a covered stent was not possible due to the location at a bifurcation. Therefore, the treatment options comprised active surveillance, selective endovascular occlusion of the afferent vessel with secondary (mild) lung infarction, or VATS lobectomy. After weighing the advantages and disadvantages of the various therapies and in compliance with the fact that patient was reluctant to undergo surgery, we mutually agreed to opt for an active surveillance approach with regular reassessment of aneurysm diameter. CT imaging at six months did not show any change in aneurysm size and patient was still free of symptoms with an unaltered chest X-ray at 12 months of follow-up. He will undergo periodic reviews in the future.

DISCLOSURES

The authors declare no conflicts of interest.

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PHOTO QUIZ

A 68-year-old man with bilateral axillary swelling

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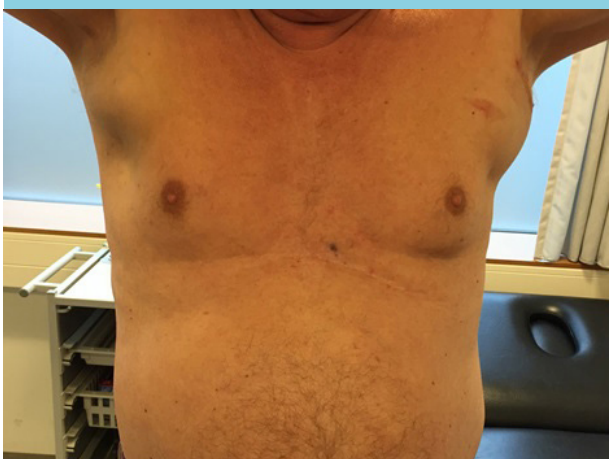
CASE REPORT

A 68-year-old Caucasian man was referred to our hospital with bilateral axillary swelling (*figure 1*). The patient had noticed lumps in his armpits four weeks ago. Under suspicion of hidradenitis suppurativa, augmentin was started, but the lumps had increased in size and started to become painful without any accompanying rubor or calor. B-symptoms were absent. Anamnestic findings included a well-treated HIV-positive partner.

Physical examination revealed a node of 7 cm in diameter in the left axilla and of 5 cm in the right axilla. Both nodes were dense and were not connected to any circumferential tissue.

Routine laboratory investigations showed an erythrocyte sedimentation rate of 49 mm/h, haemoglobin 8.7 mmol/l, leukocytes of 9.3 x 10^9/l with a normal differential count and a serum lactate dehydrogenase of 351 U/l, and transaminase activity within the normal range. A contrast-enhanced computed tomography (CT) of the neck, thorax and abdomen was performed.

Figure 1. *Bilateral axillary swelling*



WHAT IS YOUR DIAGNOSIS?

See page 352 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 351)

TITEL A 68-YEAR-OLD MAN WITH BILATERAL AXILLARY SWELLING

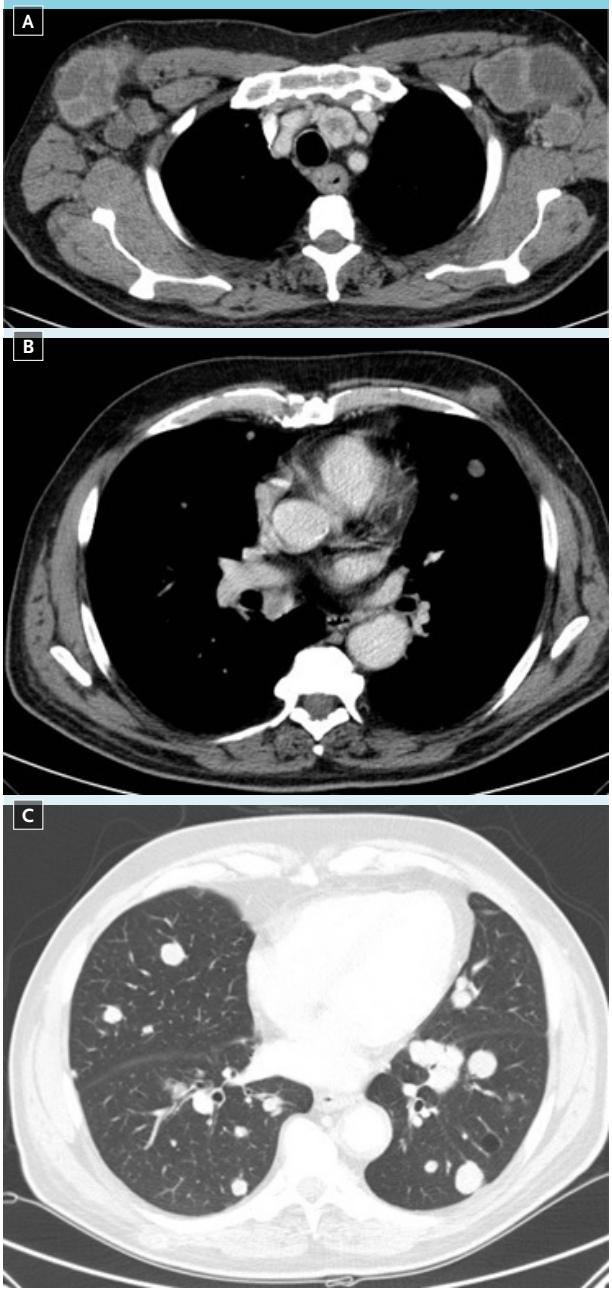
DIAGNOSIS

Radiology and histology suggested metastatic melanoma

CT scan of the thorax and abdomen revealed mediastinal and axillary lymphadenopathy with multiple metastases in the lungs and subcutis (*figure 2*). Histological material was obtained by excision of the left axillary lymph node. This revealed an undifferentiated tumour, of which the differential diagnosis included a variety of entities, such as undifferentiated carcinoma, lymphoma, neuroendocrine carcinoma and melanoma. Immunohistochemical staining showed positivity for S100 and CD56, while the tumour tested negative for leukocyte common antigen, cytokeratin and chromogranin. Additional immunohistochemistry showed that part of the cells reacted to CAM 5.2, Melan-A and HMB 45, which is compatible with the diagnosis of a melanoma (*figure 3*).[1] In retrospect the patient had noticed a naevus on his chest, close to the xiphoid process (*figure 1*), which had changed during the past few months. Biopsy of the lesion was taken and showed atypical melanocytic proliferation without any signs of epidermal involvement, thus concluding that this was a metastasis of a melanoma. Further examination of the skin by a dermatologist did not reveal any other suspicious lesions.

As far as we know, this is the first case described in the literature of a melanoma presenting with bilateral axillary metastases. In the last ten years the incidence of melanoma has almost doubled to about 5000 per year in Netherlands.[2] About 800 patients are diagnosed annually with metastatic disease stage 4. In patients without metastases or resectable stage 3 melanoma, surgical excision is the treatment of choice and can often be curative. Adjuvant treatments with targeted therapies or immunotherapies are still under investigation for high-risk patients. Treatment of unresectable cases has proven to be difficult. Treatment options for metastatic melanoma include resection, radiotherapy, chemotherapy, immunotherapy and targeted therapy depending on tumour and patient characteristics. During the last few years the development of targeted therapy and immunotherapy have led to prolonged survival compared with the conventional chemotherapeutics such as dacarbazine. The best examples of both therapies are the B rapidly accelerated fibrosarcoma (BRAF) inhibitors vemurafenib or dabrafenib and the monoclonal antibody ipilimumab, respectively. This antibody targets cytotoxic T-lymphocyte-associated protein 4 thereby enhancing anti-tumour immunity, resulting in an overall survival benefit and long-term survival in about 20% of the treated patients.[3] Vemurafenib or dabrafenib block an oncogenic cascade that is activated in approximately 50% of patients and have a response rate of about 50%, resulting in a three to four months overall survival benefit. BRAF inhibitors are registered for the treatment of patients with metastatic BRAF V600E-mutated melanoma.[4,5] Because the metastasis of the presented patient did not have a BRAF V600E mutation, he was treated with ipilimumab.

Figure 2. *Transverse CT scan of the thorax: mediastinal and axillary lymphadenopathy with metastasis in the lungs and subcutis*



Unfortunately, after two cycles of ipilimumab he presented with symptomatic brain metastases and passed away.

This case illustrates an unusual way in which melanoma can manifest. The differential diagnosis of bilateral axillary lymphadenopathy is extensive and generally implies a systemic process. It includes connective tissue disorders such as systemic lupus erythematosus and rheumatoid arthritis. Granulomatous diseases as tuberculosis and sarcoidosis are also mimickers and therefore should always be in the differential diagnosis. Infectious diseases, such as cat-scratch disease, staphylococcal or streptococcal skin infections, commonly present as tender, swollen lymph nodes near the site of inoculation. However, they are usually limited to one side and preceded by a history of local trauma, injuries or bites. As a symptom, tenderness is in most cases suggestive of a recent inflammatory process. Whereas non-tender enlarged lymph nodes point in the direction of malignancies, such as malignant lymphoma or metastasis of a solid tumour. In conclusion the presented case shows that metastases of melanoma should be considered in the differential diagnosis of a patient presenting with bilateral axillary lymphadenopathy.

Figure 3. *Histopathological presentation of the tumour: a) HE staining; b) S100; c) Melan-A; d) HMB-45. Scale bar: 50 µm*

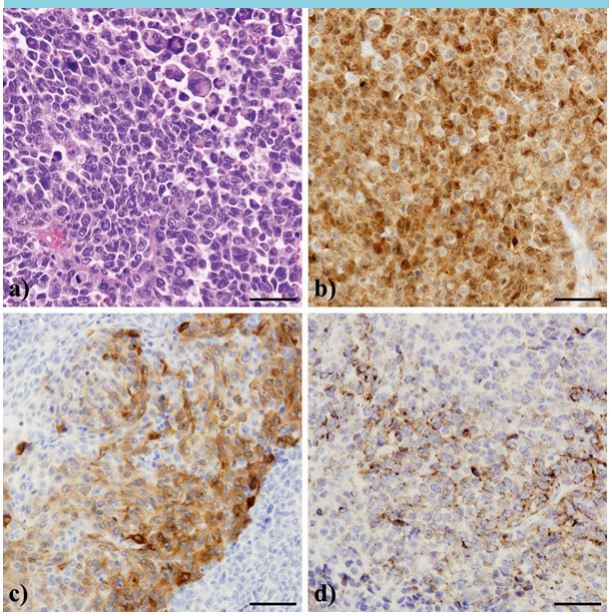


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PHOTO QUIZ

An 86-year-old patient with a slowly progressive painless swelling on his scalp

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CASE REPORT

An 86-year-old patient presented at the outpatient clinic with a painless swelling on his right frontal scalp. The swelling had been slowly progressive over the last two years. His medical history was unremarkable and no other symptoms were present. His son had noted a slight increase in irritability. Physical examination showed a painless elastic swelling (*figure 1*). Neurological examination revealed no abnormalities. Magnetic resonance imaging of the brain (*figure 2*) and a histological biopsy were performed.

WHAT IS YOUR DIAGNOSIS?

See page 355 for the answer to this photo quiz.

Figure 1. *The patient with a painless swelling on the right frontal scalp*

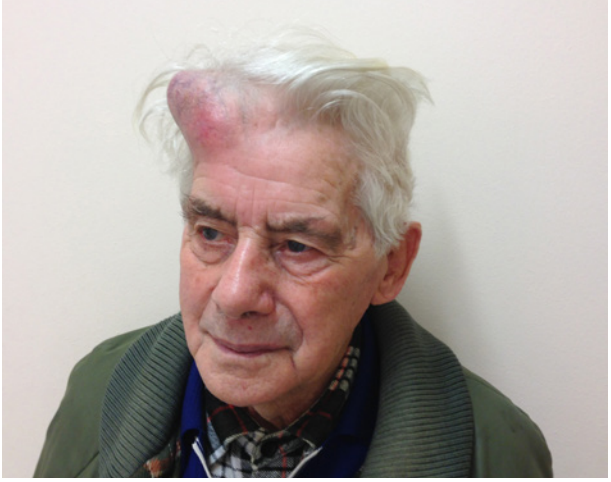
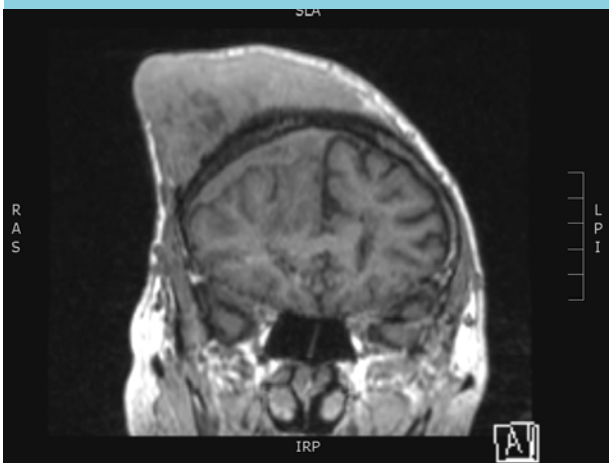


Figure 2. *MRI showing a large heterogeneous tumour located both intracranially and extracranially with mass effect and an apparently intact skull*



ANSWER TO PHOTO QUIZ (PAGE 354)

AN 86-YEAR-OLD PATIENT WITH A SLOWLY PROGRESSIVE PAINLESS SWELLING ON HIS SCALP

DIAGNOSIS

A soft-tissue sarcoma, bone metastasis of an unknown distant primary carcinoma or lymphoma was initially considered. Magnetic resonance imaging revealed a large heterogeneous tumour located both intracranially and extracranially with mass effect. The skull was apparently intact. The differential diagnosis was not revised. A histological biopsy (*figure 3*) showed an atypical meningioma (WHO grade II). Palliative treatment consisted of resection of the extracranial part of the tumour followed by 60 Gy radiotherapy in 30 fractions on the intracranial part. During surgery direct invasion of the skull was noted by the neurosurgeon. *Figure 4* shows the situation shortly after treatment. Considering the palliative intentions of the treatment, the preference and the age of the patient, no regular follow-up imaging or ambulatory visits were planned. Twelve months later the patient developed a left-sided hemiparesis and dysarthria. A CT scan showed a mass suggestive of residual/relapse meningioma. No further extracranial growth was observed. After extensive consideration of diagnostic and/or therapeutic options with the patient and his family, no further procedures were performed besides starting dexamethasone. He was entrusted into care of his general practitioner. Six months later we were informed the patient had died at home.

Meningiomas are tumours arising from the dural coverings of the brain and they are the most common primary intracranial tumour. Most meningiomas remain asymptomatic throughout life and are only found incidentally with imaging or at autopsy. Their rate of growth is typically slow. The prevalence of meningiomas found at autopsy in persons over 60 years of age is 3%, and the majority of the lesions are less than 1 cm in diameter.[1] However, progressive enlargement of the tumour can lead to focal or generalised seizure disorders or neurological deficits caused by compression of adjacent neural tissue.

The aetiology of meningioma is not well understood, although there are several recognised risk factors. The incidence is highest after the fifth decade of life. Meningiomas are twice as common in the female as in the male population. Progesterone receptors are expressed in many meningiomas and some also express oestrogen receptors. Furthermore pregnancy and menopause have been associated with an increased incidence of meningiomas suggesting an aetiological role for hormones. Cranial irradiation for intracranial tumours or disease prophylaxis has also been related to later-onset meningioma. Neurofibromatosis type 2 (NF2) is an autosomal dominant disorder due to a mutation in a tumour suppressor gene on chromosome 22, predisposing to multiple neoplastic lesions. Approximately half of the individuals with NF2 have meningiomas, often at a young age and multiple meningiomas are often present. The meningiomas seen in patients with NF2 are more frequently atypical or anaplastic compared with sporadic tumours. In addition, up to 60% of sporadic meningiomas show a somatic mutation of NF2 gene. Meningiomas can arise anywhere from the dura, most commonly within the skull and at sites of dural reflection (falx cerebri, tentorium cerebelli, venous sinuses). Other less common sites include the optic nerve sheath and choroid plexus; approximately

Figure 3. *Histopathology of biopsy specimen from scalp. There is a mixed architectural pattern with 10-20 mitotic figures per 1.6 mm², increased cellularity, small cells with a high ratio of nucleus to cytoplasm and prominent nucleoli. (H&E, magnification 400x)*

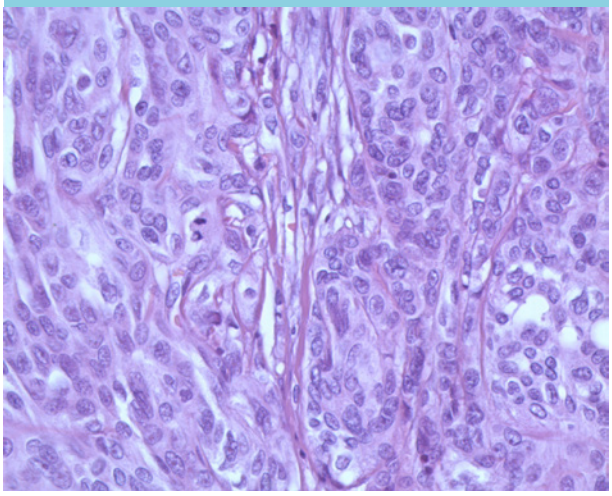


Figure 4. *The patient shortly after treatment*

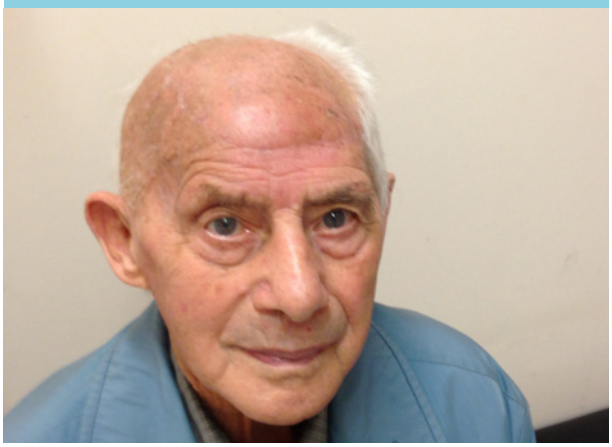


Table 1. *WHO classification of meningiomas*

	WHO grade I	WHO grade II	WHO grade III
Frequency	About 90%	5-7%	1-3%
Architectural pattern	Meningothelial, psammomatous, secretory, fibroblastic, angiomatous, lymphoplasmacyte-rich, transitional, microcystic, metaplastic	Clear-cell, chordoid, atypical	Papillary, rhabdoid, anaplastic
Histological	No signs of atypical or malignant growth	≥4 mitotic figures per 1.6 mm^2 or ≥3 of the following features: increased cellularity, small cells with a high ratio of nucleus to cytoplasm, prominent nucleoli; sheet-like growth pattern; geographic necrosis	≥20 mitotic figures per 1.6 mm^2, obvious malignant cytology
Biological behaviour	Can infiltrate in dura, venous sinuses, bone, orbit, soft tissue and skin	Can infiltrate in brain tissue.	Infiltrates in brain tissue

10% arise in the spine. Very rarely, meningiomas can arise at extradural sites.

Histological grading of meningiomas is based on the WHO classification (*table 1*). Most (about 90%) are WHO grade I, reflecting their benign nature. Atypical meningiomas (WHO grade II) make up 5-7% and anaplastic variants (WHO grade III) 1-3%. Patients with WHO grade II or grade III meningiomas are more likely to have invasive disease, a local recurrence following the initial treatment, and ultimately to have a shorter overall survival compared with patients with a WHO grade I meningioma. Individual management of patients with a meningioma depends on the signs and symptoms, age, WHO grade, site and size of the tumour. Most patients with small asymptomatic meningiomas can be safely observed. Symptomatic meningiomas and asymptomatic tumours that are expanding, infiltrating, or associated with surrounding oedema should be surgically resected if feasible. Radiation therapy can be used after incomplete resection, after recurrence and when tumour histology reveals atypia or anaplasia.[2] Extracranial meningiomas are rare and the majority have a secondary extension of the primary intracranial tumour through the skull, without radiological evidence of osteolysis.[3]

In conclusion, meningiomas are mostly benign intracranial lesions and extracranial extension of atypical meningioma is rare. Management should be tailored depending on the patients characteristics and wishes and difficulties in decision-making may arise.

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LETTER TO THE EDITOR

Infliximab for treatment of pyoderma gangrenosum

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Dear Editor,

We read with interest the article by Bakelants and colleagues on the diagnosis and treatment of pyoderma gangrenosum.[1] In the last part of their discussion, they mentioned a single dose of infliximab as one of the novel treatments of pyoderma gangrenosum. This treatment is noticeable as tumour necrosis factor is one of the important mechanisms in the pathogenesis of this skin disorder.[2]

As treatment of this disorder is sometimes very difficult with a high rate of recurrence and slow healing, we would like to emphasise that although a single dose of infliximab may have a beneficial effect in nearly 50% of cases, complete remission only occurs in 21% of cases after two doses of infusion of infliximab.[3] Many patients need to continue the drug intermittently to attain complete healing.[4]

In our own experience with infliximab in the treatment of pyoderma gangrenosum associated with inflammatory bowel disease, especially in cases with extensive disease, we had to continue the drug for up to two years to achieve complete remission. This drug has promising results if used in an appropriate dose, for an appropriate time and with the appropriate precautions.[5] Otherwise the failure rate would be high. The duration of treatment needs to be individualised based on the extent of the pyoderma gangrenosum and the response rate. Even with an initial response, the drug might need to be continued to prevent recurrence which has a high rate.

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