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CLINICAL STUDY

Absence of major fibrotic adverse events in hyperprolactinemic patients treated with cabergoline

M Lafeber¹, A M E Stades¹, G D Valk¹, M J Cramer², F Teding van Berkhout³ and P M J Zelissen¹

Departments of ¹Internal Medicine and Endocrinology, ²Cardiology and ³Respiratory Medicine, University Medical Center Utrecht, Room Number L 00.408, PO Box 85500, 3508 GA Utrecht, The Netherlands

(Correspondence should be addressed to P M J Zelissen; Email: p.m.j.zelissen@umcutrecht.nl)

Abstract

Background: Cabergoline, a dopamine agonist used to treat hyperprolactinemia, is associated with an increased risk of fibrotic adverse reactions, e.g. cardiac valvular fibrosis, pleuropulmonary, and retroperitoneal fibrosis.

Objective: This study evaluated the prevalence and risk of fibrotic adverse reactions during cabergoline therapy in hyperprolactinemic and acromegalic patients.

Design: A cross-sectional study was conducted in a University Hospital.

Patients: A total of 119 patients with hyperprolactinemia and acromegaly who were on cabergoline therapy participated in the study.

Methods: All patients were requested to undergo a cardiac assessment, pulmonary function test, chest X-ray, and blood tests as recommended by the European Medicine Agency. Matched controls were recruited to compare the prevalence of valvular regurgitation. Cardiac valvular fibrosis was evaluated by assessing valvular regurgitation and the mitral valve tenting area (MVTa). The risk of pleuropulmonary fibrosis was assessed by a pulmonary function test, a chest X-ray, and if indicated, by additional imaging studies.

Results: The prevalence of clinically relevant valvular regurgitation was not significantly different between cases (11.3%) and controls (6.1%; $P=0.16$). The mean MVTa was 1.27 ± 0.17 and 1.24 ± 0.21 cm² respectively ($P=0.54$). Both valvular regurgitation and the MVTa were not related to the cumulative dose of cabergoline. A significantly decreased pulmonary function required additional imaging in seven patients. In one patient, possible early interstitial fibrotic changes were seen. Lung function impairment was not related to the cumulative cabergoline dose.

Conclusion: Cabergoline, typically dosed for the long-term treatment of hyperprolactinemia or acromegaly, appears not to be associated with an increased risk of fibrotic adverse events.

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Introduction

The treatment of choice for prolactinomas is the administration of a dopamine receptor agonist. The long-acting ergot-derived D2-selective dopamine agonist cabergoline is frequently prescribed in this condition because of superiority in terms of both tolerability and efficacy compared with various other agents (1, 2). Cabergoline is also used in acromegaly as an adjunctive agent for lowering GH levels (3).

Recently, the association between long-term ergot-derived dopamine agonist therapy and cardiac valvular fibrosis was reported. This increased risk of fibrotic valvular disease was initially reported in patients with Parkinson's disease using pergolide, bromocriptine, or cabergoline (4, 5). In these patients, a relation between both the cumulative dose and duration of cabergoline treatment and valvular thickening causing clinically

significant regurgitation was confirmed in several studies (6). Other reports have indicated a possible increased risk of pericardial, pleuropulmonary, and retroperitoneal fibrotic reactions after the use of ergot-derived dopamine agonists (7–9). Subsequently, the Committee on Safety of Medicines issued warnings about these possible adverse reactions, and recommended screening tests including pulmonary function tests during chronic dopamine agonist treatment (10).

Although data derived from patients treated for Parkinson's disease cannot be extrapolated to prolactinoma patients due to differences in the patients' age, gender, and daily cabergoline dose, concerns have been raised about cabergoline use in patients with hyperprolactinemia. Currently, several studies evaluating cardiac valvular disease in prolactinoma patients have reported inconsistent results. So far, clinically relevant valvular regurgitation has not been found (11–18).

Results of screening procedures for other fibrotic adverse reactions, such as pleuropulmonary and retroperitoneal fibrosis, in patients treated for hyperprolactinemia with cabergoline are not yet reported.

Recently, the European Medicine Agency recommended screening cabergoline-treated patients not only for signs of cardiac valvular fibrosis, but also for pleuropulmonary and retroperitoneal fibrosis because of the safety concerns. This study evaluated the prevalence and risk of fibrotic adverse reactions of the heart valves, lungs, and retroperitoneum during cabergoline therapy in a large cohort of patients with hyperprolactinemia or acromegaly.

Patients and methods

Study population

All records of patients with a prolactinoma, hyperprolactinemia, or acromegaly on cabergoline therapy for at least 6 months were retrieved from the hospital administration of the University Medical Center Utrecht. All identified patients were invited to undergo tests to identify possible fibrotic adverse reactions.

To compare the prevalence of valvular regurgitation, the prevalence of valvular regurgitation in cases was compared with the prevalence in control subjects matched for gender and age (± 2 years). The control subjects were healthy recreational athletes or patients sent for ultrasonic evaluation after a cerebral hemorrhage or an episode of palpitations, who were selected from an echocardiographic database. The control subjects with cerebral hemorrhage were included if they did not have stunned myocardium syndrome (an abnormal cardiac morphology or signs of ventricular systolic function). Control subjects with palpitations were only included if they were found to have a sinus rhythm with normal left ventricular dimensions and systolic function. By selecting control subjects in this manner, the prevalence of valvular regurgitation of control subjects is not expected to be overestimated. Both cases and controls were excluded from the analysis of data if they had a history of myocardial infarction within the past year, rheumatic fever, endocarditis, connective tissue disease, carcinoid syndrome, thyrotoxicosis, and Parkinson's disease.

The results of pulmonary function tests were compared with the individual predicted values according to the standard tables validated in large studies (19, 20).

The follow-up of the patients included in this study was part of regular medical care. The approaches described in this paper did not involve any randomization and experimental intervention, and the anonymity of patients was not breached. The Medical Ethics Review Committee of our hospital concluded that the Medical Research Involving Human Subjects Act

(WMO) is not applicable since this article meets the required conditions under Dutch Law (WGBO) for making medical and/or personal data available for statistical or other scientific research.

Data collection

All patients received a questionnaire asking for complaints such as dyspnea, coughing, chest pain, and pain in the loins. Furthermore, the patients were asked to report previous use of drugs such as ergotamine, methysergide, and (dex)fenfluramine.

The total cumulative dose and the duration of use of cabergoline were calculated from data derived from the records of each patient. The cumulative dose of cabergoline was calculated as weekly doses used multiplied by the number of weeks of treatment from the beginning of the treatment until the day of the assessment.

Blood samples were evaluated for erythrocyte sedimentation rate (ESR; reference value males: 1–5 mm/h, females: 2–12 mm/h), C-reactive protein (CRP; reference value: 1–10 mg/l), and creatinine concentration (reference value males: 74–120 $\mu\text{mol/l}$, females: 58–103 $\mu\text{mol/l}$). The estimated glomerular filtration rate (eGFR) was calculated by making use of the Modification of Diet in Renal Disease formula (21). The prolactin concentration before initiation of therapy was collected from the medical records.

Cardiac assessment

Evaluation of complete medical and cardiac history including smoking habits; a physical examination with measurement of height, weight, and blood pressure; and electrocardiography were performed in every patient.

A transthoracic echocardiography (TTE) was carried out by a non-blinded, trained operator using a commercially available system ('Vivid S6'; GE Vingmed ultrasound, General Electric, Milwaukee, WI, USA) with particular attention being paid to valvular function in both cases and controls. TTE was performed with the subject at rest, lying in left lateral decubitus position. M-mode, 2D images, and color flow Doppler recordings, triggered to the QRS complex, were obtained using a 2.5–5.0 MHz transducer with 'smart depth' function in the parasternal (long and short axes) and apical (two and four chambers, long axis) views in accordance with the American Echocardiography Society/European Association of Echocardiography guidelines (22). The images were stored in cine-loop format (EchoPAC PC version 7.0.0, GE Vingmed Ultrasound) for off-line analysis. The TTE images from both cases and controls were independently reviewed by one experienced observer blinded to the patients' medical history.

Valvular regurgitation was graded according to the combined American and European guidelines as absent (grade 0), physiological trace (grade 1), mild (grade 2), moderate (grade 3), or severe

(grade 4) (23). The previously defined US Food and Drug Administration (FDA) criteria of aortic regurgitation of mild or greater severity and pulmonary, tricuspid, and mitral regurgitation of moderate or greater severity were used to determine the clinically relevant valvular regurgitation (24). All individual outcomes and the combined endpoint of all clinically significant outcomes were studied. Additionally, the mitral valve tenting area (MVTa) was measured. The MVTa is defined as the area enclosed between the atrial surface of the valve leaflets and a line connecting juxtaposed points on the anterior and posterior mitral annuli. This area was traced in parasternal long-axis view during end-systole. The MVTa is an index of valvular leaflet stiffening and apical displacement of leaflet coaptation, which may reveal early valve changes leading to regurgitation (25). The inter-observer variability of regurgitation grading was evaluated in a random sample of cases (15%), and it resulted in a mean kappa of 0.86. Reassessment of the MVTa in a sample of the cases resulted in a correlation coefficient of 0.85.

Pulmonary assessment

The pulmonary function tests were performed by trained employees. They included measurement of vital capacity (VC) and total lung capacity (TLC) using a constant-volume body plethysmograph with diffusion capacity monitoring using carbon monoxide (DL_{CO}) as measured by the single-breath technique performed according to the American Thoracic Society standards (26, 27). Unlike many parameters, for which normal values are not correlated with the characteristics of a case, predicted values of pulmonary function depend upon the patient's age, height, gender, and race. Therefore, to interpret the pulmonary function tests, these factors must be taken into consideration. All measurements were transcribed into the percentage of the predicted value obtained from standard tables for the patients' sex, age, race, weight, and length (19, 20). The normal range for the measurements of pulmonary function is 80–120% of the predicted value. Therefore, lung function was regarded as abnormal when the measured lung volume (VC and/or TLC) was <80% of the predicted value, and/or the DL_{CO} was <75% in females and 80% in males. Pleural fibrosis could result in a restrictive pulmonary function test with a decreased VC and/or TLC. However, pulmonary fibrosis, characterized by fibrosis in the alveoli, would result in diffusion-impaired pulmonary function test with a decreased DL_{CO} . All lung function tests were reviewed by a pulmonologist blinded to the patients' medical history. Patients with an abnormal initial pulmonary function test result were requested to undergo a second pulmonary function test. The result of the pulmonary function test was graded as abnormal if it was indicated so by both measurements.

Furthermore, a chest X-ray was performed in every patient to assess the presence of major fibrotic interstitial or pleural changes such as pleural thickening.

Additional diagnostic tests

Additional diagnostic tests were recommended to patients with abnormal test results after consensus was obtained during expert consensus meetings. A computed tomography (CT) scan of the retroperitoneum to exclude retroperitoneal fibrosis was performed if there was an unexplained elevation of ESR, CRP, or creatinine, and if the patient had complaints of pain in the abdomen or loins, or if edema of the legs was present. In patients with abnormal pulmonary function test results and/or an abnormal chest X-ray, a high-resolution (HR) pulmonary CT scan of the chest was performed to assess possible fibrotic changes. In patients with no complaints but borderline abnormal pulmonary test results, probably due to difficulties in the single-breath technique or due to obesity, no additional diagnostic tests were performed.

Statistical analysis

The data of the cases and controls were analyzed using SPSS 15.0 software for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean and s.d. ($x \pm s.d.$) or as median and range. Categorical variables are presented as a percentage of the total ($n(\%)$). Differences between groups have been tested with (non) parametric tests, e.g. Student's two-sided *t*-test for continuous variables and the χ^2 tests for categorical variables. Differences between the two groups have been tested with ANOVA. To correlate the clinical variables such as cumulative dose, gender, age, and body mass index (BMI) with the findings during cardiac assessment and functional lung testing, linear regression analysis was used. All results have been considered to be statistically significant if the *P* value is <0.05.

Results

Clinical characteristics

In total, 121 patients on (previous) cabergoline therapy were identified. Two patients were excluded because of a history of carcinoid syndrome and connective tissue disease. All the remaining 119 patients were included. The baseline characteristics are displayed in Table 1. The study population consisted of 94 patients with a prolactinoma, 14 patients with acromegaly and secondary hyperprolactinemia, five patients with a combined prolactin/GH-producing adenoma, and six patients with a non-secreting pituitary tumor with secondary hyperprolactinemia. In total, 110 (92.4%)

Table 1 Baseline characteristics.

Variable	Outcome
Number of patients; <i>n</i>	119
Male sex; <i>n</i> (%)	60 (50.4)
Age (years); mean \pm s.d.	50.3 \pm 14.7
BMI (kg/m ²); mean \pm s.d.	25.2 \pm 5.4
Highest pre-treatment PRL level (IE/L); median (range)	10.0 (0.1–626)
Disease duration (years); mean \pm s.d.	11.8 \pm 9.4
Diagnosis	
Prolactinoma; <i>n</i> (%)	94 (78.9)
Acromegaly with secondary hyperprolactinemia; <i>n</i> (%)	14 (11.8)
Combined prolactinoma and acromegaly; <i>n</i> (%)	5 (4.2)
Stalk compression with hyperprolactinemia; <i>n</i> (%)	6 (5.0)
Size of the tumor	
Microadenoma (< 10 mm); <i>n</i> (%)	24 (20.2)
Macroadenoma (> 10 mm); <i>n</i> (%)	95 (79.8)
Cabergoline	
Total cumulative dose (mg); median (range)	277 (16–3385)
Total duration of use (months); median (range)	115 (7–551)
Mean weekly dose (mg); median (range)	1.0 (0.25–12.0)
Blood pressure	
Systolic blood pressure (mmHg); mean \pm s.d.	140 \pm 22
Diastolic blood pressure (mmHg); mean \pm s.d.	86 \pm 10
Hypertension	33 (27.7)
Examinations performed	
Questionnaire; <i>n</i> (%)	113 (95.0)
Blood samples; <i>n</i> (%)	114 (95.8)
Cardiac screening; <i>n</i> (%)	115 (96.6)
Pulmonary function tests; <i>n</i> (%)	113 (95.0)
Chest X-ray; <i>n</i> (%)	112 (94.2)

patients had controlled disease with prolactin levels within the range of the reference value (28).

The median weekly dose of cabergoline was 1.0 mg (range 0.25–12.0). The median cumulative cabergoline dose was 277 mg (range 16–3385 mg). The median duration of cabergoline use was 115 months (range 7–551 months).

The reported complaints and laboratory results are displayed in Table 2. ESR was increased in almost half of the patients (47.2%), but it increased more than three times the upper limit in 11 (9.6%) patients. In five patients, the ESR normalized after repeated measurements. In three cases, repeated ESRs were missing, but elevated ESR could be explained by co-morbidity, and three cases had an additional CT scan of the lungs and/or abdomen that showed no abnormalities indicative of fibrotic complications. CRP was increased in five cases (4.4%). The eGFR was decreased (60–30 ml/min per 1.73 m²) in ten patients (8.8%). There was no significant association between the reported complaints or laboratory blood results and the cumulative dose of cabergoline either in the total population or in the patient subgroups, even after adjusting for age and/or gender.

Cardiac assessment

The mean blood pressure was significantly higher in the cases (systolic: 140 \pm 22, diastolic: 86 \pm 10 mmHg) than in the controls (systolic 135 \pm 20 mmHg; *P*=0.05, diastolic: 80 \pm 10 mmHg; *P*=0.001). The BMI was significantly higher in the patients (25.2 \pm 5.4 kg/m²) than in the controls (24.4 \pm 3.3 kg/m², *P*=0.005). The prevalence of valvular regurgitation is displayed in Table 3. In total, 13 cases (11.3%) had a clinically significant valvular regurgitation. Eight prolactinoma and two acromegalic patients had mild aortic regurgitation (grade 2), and two acromegalic patients had a moderate aortic regurgitation (grade 3). One prolactinoma patient was diagnosed with a moderate tricuspid regurgitation (grade 3). The prevalence of clinically relevant valvular regurgitation was not significantly different between cases and controls (*P*=0.16). This finding was identical in the group of patients with a prolactinoma compared with the controls, 9 vs 6 respectively (*P*=0.42), and in the group of patients with acromegaly compared with the controls, 4 vs 1 respectively (*P*=0.34). The mean cumulative dose of cabergoline in the group of patients with clinically relevant valvular regurgitation, 423 mg, did not differ from the cumulative dose in those without clinically relevant regurgitation, 466 mg (*P*=0.26). Clinically relevant regurgitation was not related to the cumulative dose of cabergoline, even after adjusting for possible confounders such as age, gender, smoking habit, and BMI. Relevant regurgitation was more prevalent in male cases than in male controls; six prolactinoma and three acromegalic patients versus two controls (*P*=0.03). The cumulative dose did not significantly differ in the males with (339 mg) and without (546 mg) relevant regurgitant valves (*P*=0.37). The prevalence of regurgitation in the individual valve type did not differ between males and females in either cases or controls, though a trend was seen for mild aortic regurgitation in male patients compared with male controls, 7 vs 2 respectively (*P*=0.09).

Table 2 Reported complaints, laboratory blood results, and pulmonary function test results.

Variable	Outcome
Laboratory evaluation (<i>n</i> =114)	
ESR > 3 \times upper limit; <i>n</i> (%)	11 (9.6)
CRP > upper limit; <i>n</i> (%)	5 (4.4)
Creatinine > upper limit; <i>n</i> (%)	5 (4.4)
eGFR 60–30 ml/min per 1.73 m ² (MDRD); <i>n</i> (%)	10 (8.8)
Pulmonary function test (<i>n</i> =113)	
VC (percentage of individual predicted VC); mean \pm s.d.	106 \pm 15
TLC (percentage of individual predicted VC); mean \pm s.d.	99 \pm 16
DL _{CO} (percentage of individual predicted VC); mean \pm s.d.	91 \pm 14

Table 3 Prevalence of valvular regurgitation by valve type and mitral valve tenting area.

Variable	Patients (n=115)	Controls (n=115)
Clinically significant valvular regurgitation; n (%)	13 (11.3)	7 (6.1)
Aortic regurgitation		
Absent/physiological trace; n (%)	100 (87.0)	107 (93.0)
Mild; n (%)	10 (8.7)	6 (5.2)
Moderate; n (%)	2 (1.7)	0 (0)
Severe; n (%)	0 (0)	0 (0)
Missing; n (%)	3 (2.6)	2 (1.7)
Pulmonary regurgitation		
Absent/physiological trace; n (%)	74 (64.3)	76 (66.1)
Mild; n (%)	10 (8.7)	14 (12.2)
Moderate; n (%)	0 (0)	0 (0)
Severe; n (%)	0 (0)	0 (0)
Missing; n (%)	31 (27.0)	22 (19.1)
Mitral regurgitation		
Absent/physiological trace; n (%)	101 (87.8)	104 (90.4)
Mild; n (%)	11 (9.6)	11 (9.6)
Moderate; n (%)	0 (0)	0 (0)
Severe; n (%)	0 (0)	0 (0)
Missing; n (%)	3 (2.6)	0 (0)
Tricuspid regurgitation		
Absent/physiological trace; n (%)	81 (70.4)	78 (67.8)
Mild; n (%)	27 (23.5)	31 (27.0)
Moderate; n (%)	1 (0.9)	1 (0.9)
Severe; n (%)	0 (0)	0 (0)
Missing; n (%)	10 (8.7)	5 (4.3)
Mitral tenting area (cm ²); mean ± s.d.	1.27 ± 0.17	1.25 ± 0.21

The mean MVTA was 1.27 ± 0.17 cm² in patients and 1.24 ± 0.21 cm² in the controls ($P=0.54$). The mean MVTA was 1.27 ± 0.18 cm² in prolactinoma patients versus 1.23 ± 0.21 cm² in controls ($P=0.20$) and 1.21 ± 0.10 cm² in acromegalic patients versus 1.34 ± 1.21 cm² in controls ($P=0.09$). The MVTA was not correlated with the cumulative dose of cabergoline in the different patient subgroups, not even after correcting for age, gender, smoking habit, or BMI.

Pulmonary assessment

The results of the pulmonary function test of all patients are displayed in Table 2. In total, eight patients' pulmonary function test results were regarded as abnormal. In two cases, this was due to a decreased lung volume/capacity; in five cases, this was due to a decreased DL_{CO}; and in one case, this was due to a combination of both. In five cases, the abnormal pulmonary function test result could not be explained, and additional diagnostic tests were performed. The presence of an abnormal pulmonary function test result was not associated with the cumulative dose of cabergoline. Only the measured percentage of the predicted TLC was significantly inversely correlated with the cumulative dose of cabergoline after adjusting for BMI ($R=0.48$, $P=0.007$). Age, gender, and smoking habits were not correlated with the TLC.

In total, six patients had signs of minimal pleural thickening on the chest X-ray. There was no association with an abnormal pulmonary function test, reported pulmonary complaints or the cumulative dose of

cabergoline. Furthermore, the lung volume, diffusion capacity, and chest X-rays were not correlated with the presence of clinically relevant valvular regurgitation.

Additional diagnostic tests

The indications for and results of the additional diagnostic tests are displayed in Table 4. In total, six thoracic HR thoracic CT (HR-CT) scans and two abdominal CT scans were performed. A HR-CT scan in a 66-year-old male with a decreased DL_{CO} showed bilateral shading of the interlobair and interlobular septae. This may indicate early pulmonary fibrosis. The cumulative dose of cabergoline of this patient (236 mg) did not differ from the mean dose of the total population. The CT scans in the remaining patients showed no pathology. Only case number 6 also had significant valvular regurgitation (mild aortic regurgitation). A male prolactinoma patient of 43 years of age had an elevated ESR (27 mm/h), which could not be explained by co-morbidity and did not decrease after repeated measurements. The abdominal CT scan showed no signs of fibrosis.

Discussion

To our knowledge, this is the largest study assessing possible fibrotic events in hyperprolactinemic and acromegalic patients treated with cabergoline, and it is the first study also assessing clinically relevant fibrotic adverse reactions other than valvular pathology.

Table 4 Additional diagnostic test results.

No.	Age (years)	Sex	Diagnose	Cumulative dose (mg)	Complaints	Blood testing	Pulmonary function testing	Chest X-ray	Additional diagnostic tests
1	71	F	ACR	967	Edema	ESR↑ (37)	VC↓ (72%), TLC↓ (69%), DL _{CO} ↓ (60%) DL _{CO} ↓ (71%)	Right interlobium thickening	HR-CT: normal
2	58	M	PRL	290	Chest pain, dyspnea	Normal	DL _{CO} ↓ (60%) DL _{CO} ↓ (71%)	Normal	HR-CT: normal
3	59	M	PRL	348	Chest pain, dyspnea	Normal	DTL _{CO} ↓ (76%)	Normal	HR-CT: normal
4	66	M	PRL	236	Chest pain, dyspnea, coughing	ESR↑ (14)	DL _{CO} ↓ (75%)	Normal	HR-CT: shading of the interlobair and -lobular septae
5	28	F	PRL	412	None	Normal	DL _{CO} ↓ (75%)	Normal	HR-CT: normal
6	54	M	PRL	519	Edema	ESR↑ (51)	Normal	Bilateral pleural thickening	HR/ABD CT: normal

ACR, acromegaly; PRL, prolactinoma; ESR, erythrocyte sedimentation rate; VC, vital capacity; TLC, total lung capacity; DL_{CO}, pulmonary diffusion capacity; HR-CT, high-resolution thoracic computed tomography; ABD-CT, abdominal computed tomography.

We found no increased risk of valvular regurgitation of any grade in hyperprolactinemic patients using cabergoline. Clinically relevant regurgitation was not diagnosed significantly more in patients than in controls. Severe regurgitation was not seen in any of our patients or controls, and moderate valvular regurgitation was seen only in 2.6% of the patients. Mild aortic regurgitation was numerically seen more often in male patients compared with the controls, though this was not a significant finding. It is noteworthy that, in the selection of the control population, relatively healthy controls were selected, and patients with major morphological cardiac abnormalities were not included to assure a 'normal population'. This might have led to an underestimation of the prevalence of valvular regurgitation in the controls. As a consequence, the observed effect of cabergoline treatment on the cardiac valves could be overestimated. Still, we did not find a significant effect of cabergoline on cardiac valve function in all individual measurements and the combined endpoint.

Furthermore, concerning the prevalence of pleuro-pulmonary adverse events, only one patient showed possible early signs of pulmonary fibrosis. This significant correlation between the cumulative dose and TLC after adjusting for BMI could be a coincidental finding due to multiple testings without clinical relevance. This finding awaits further research to confirm and clarify the meaning of this correlation. Other parameters of pulmonary functions (VC, DL_{CO}) showed no relation with cabergoline therapy. Indications for additional diagnostic tests for retroperitoneal fibrosis were not found in our population. Therefore, the risk of clinically relevant fibrosis does not seem to be seriously increased.

The prevalence of regurgitant valves in our cases and controls is comparable to that observed in a previous population-based cohort study (29). Nonetheless, visual grading of regurgitation of the cardiac valves is subject to a degree of inter- and intra-observer variability (30–32). In the present study, both cases and controls were reviewed by a single blinded and independent expert, thereby excluding inter-observer variability. Furthermore, the 15% random sample of the cases showed a kappa of 0.86 for grading regurgitation and a correlation coefficient of 0.85 for the MVTa, demonstrating a high degree of intra-observer agreement.

Significant evidence exists that cabergoline therapy in patients with Parkinson's disease is associated with an increased risk of developing valvular fibrosis (4, 5, 33). However, as mentioned before, several main differences between hyperprolactinemic and Parkinson's disease patients should be taken into account when evaluating the risks of fibrotic adverse reactions. Patients with Parkinson's disease are mostly of older age, predominantly male, and are treated with a much higher cabergoline dose (34). The study conducted on Parkinson's disease patients reported a mean daily cabergoline dose of 3.6 mg, whereas the median weekly

dose in our cohort was 1.0 mg (5). Therefore, in Parkinson's disease patients, the mean cumulative dose is far higher, 2500–6600 mg, compared with hyperprolactinemic patients (33).

Identical to our results, five of eight previous publications evaluating valvular regurgitation in hyperprolactinemic patients on cabergoline therapy found no increased risk of valvular regurgitation of any grade (11, 13, 15–17). Among the remaining studies, one reported a significantly increased prevalence of mild tricuspid regurgitation in cabergoline-treated patients and the other reported an increased prevalence of mild tricuspid and pulmonary regurgitation (14, 18). However, both mild tricuspid and pulmonary regurgitation are not considered to be clinically relevant findings (24). The increased prevalence of clinically relevant regurgitation/aortic regurgitation in male cases was not reported before.

Our analyses were conducted and reported for both hyperprolactinemic patients and acromegalic patients, although it is known that in acromegaly, the prevalence of cardiac and valvular pathology is increased. The prevalence of valvular pathology among our cabergoline-treated acromegaly patients was high (4 of 19 patients), but it was not significantly increased compared with the controls. Our finding is possibly due to small numbers. Another cohort of 40 patients with acromegaly, though uncorrected for cabergoline therapy, reported a significantly increased prevalence of valvular disease (22%) compared with the controls (6.7%) (35). Acromegaly patients were also included in this study, because these patients use cabergoline as adjunct treatment infrequently, and should therefore not be excluded in these analyses.

An increased risk of clinically relevant, moderate tricuspid regurgitation was reported by a single study (12). In total, 27 of the 50 (54%) hyperprolactinemic patients on cabergoline therapy were diagnosed with a moderate tricuspid regurgitation compared with 9 of the 50 (18%) controls. Furthermore, a cumulative dose of more than the median, 280 mg, was associated with an increased prevalence of tricuspid regurgitation compared with a lower cumulative dose. However, the reported prevalence of moderate tricuspid regurgitation in both cases and controls is at least tenfold of the reported population-based prevalence, which raises questions concerning observer variability of grading regurgitation (29).

In contrast to cardiac valvular fibrosis, the current evidence is poor for cabergoline-related pleuropulmonary and retroperitoneal fibrosis. In clinical practice, the diagnosis of pulmonary fibrosis is based on pulmonary function tests, chest imaging studies, and histological assessments (28, 36). Elevated ESR is of limited value in making the diagnosis of fibrosis (37). Currently, there is no validated (bio)marker of early pleuropulmonary fibrosis. Therefore, we primarily used pulmonary function tests to assess the pulmonary status.

Only in high-risk patients were additional imaging studies performed due to an impaired pulmonary function. Early stages of pleuropulmonary fibrosis therefore could be missed. However, the object of interest was mainly to assess the prevalence of clinically relevant pulmonary fibrosis.

Recently, one study suggested that cabergoline use is potentially associated with pleuropulmonary and retroperitoneal fibrosis by identifying reports of fibrotic adverse reactions within the US Adverse Event Reporting System database (7). Several case reports showed patients with pulmonary fibrosis confirmed by a pulmonary function test and HR chest CT scan after cabergoline treatment (38–41). Identical articles have been published with regard to the association of pulmonary fibrosis and other dopamine agonists. Nevertheless, the prevalence of relevant fibrotic pleuropulmonary and retroperitoneal disease is unknown. Our study indicates that there is no seriously increased risk of clinically relevant pleuropulmonary or retroperitoneal fibrosis in hyperprolactinemic and acromegaly patients.

The proposed mechanism of fibrotic adverse reactions is the activation of the 5-hydroxytryptamine 2B (5-HT_{2B}) receptor inducing both proliferative and fibrotic signals in various mesothelial cell types. Excessive proliferation of fibrocytes could lead to overgrowth valvopathy, but in theory, it could also lead to pleuropulmonary and retroperitoneal fibrosis (42–44). The potent 5-HT_{2B} receptor agonistic characteristic of cabergoline seems to be the key in the pathogenic cascade, and it is likely to be a drug class effect. If fibrotic adverse reactions are mediated by the activation of the 5HT_{2B} receptor, a correlation between the (cumulative) dose and the fibrotic effects would reasonably exist (44). In patients with Parkinson's disease, the cumulative dose was indeed associated with valvular disease and the MVTa (5, 34). However, we could not demonstrate an association between the cumulative cabergoline dose and valvular regurgitation along with the results of seven of eight studies conducted in hyperprolactinemic patients (11–18). We found no increased MVTa or association between the MVTa and the cumulative cabergoline dose. One of two studies found a significantly increased MVTa in patients treated with cabergoline; however, no association was found with the cumulative dose (13, 15). These contradicting findings suggest that a certain critical threshold of cumulative cabergoline dose for the development of fibrosis exists.

Furthermore, the way in which the cumulative dose is reached could play a role. The total cumulative dose is a function affected by the dimensions of both time and dose. In patients with Parkinson's disease, the duration of treatment is limited, but the daily dose is relatively high, whereas hyperprolactinemic patients are treated for a longer period of life with a far lower dose. It could be hypothesized that a high dose of cabergoline

increases the risk of fibrosis significantly more than a treatment given for a long duration. This is supported by the finding in Parkinson's patients that the risk of valvular regurgitation was, in particular, increased in patients receiving at least 3 mg of cabergoline daily for a minimum of 6 months (4, 5).

Understandably, concerns still exist that long-term use of cabergoline may also lead to fibrotic adverse reactions in hyperprolactinemic patients. However, data derived from this study and previous publications seem to be reassuring. Cabergoline, typically dosed for the long-term treatment of hyperprolactinemia, is not associated with a seriously increased risk of relevant fibrotic adverse reactions. Therefore, unfounded fear of the long-term effect of cabergoline should not result in inappropriate cessation of successful treatment with cabergoline.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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