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Assessment of cardiac valve dysfunction in patients receiving cabergoline treatment for hyperprolactinaemia

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1 1 **Assessment of cardiac valve dysfunction in patients receiving cabergoline treatment for**
2
3 2 **hyperprolactinaemia**

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13 12 Abbreviated title: Cabergoline and valvular heart disease

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19 18 Key words: hyperprolactinaemia, prolactinoma, dopamine agonist, valvulopathy, cabergoline,
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21 20
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1 1 **Abstract**

2
3 2 *Objective:*

4 3 Cabergoline is a highly effective medical treatment for patients with hyperprolactinaemia. There is an
5
6 4 increased risk of valvular heart disease in patients receiving cabergoline for Parkinson's disease. This study
7
8 5 examined whether cabergoline treatment of hyperprolactinaemia is associated with a greater prevalence of
9
10 6 valvulopathy.

11
12 7 *Design:*

13 8 Cross-sectional, two-dimensional echocardiographic study performed by a single echocardiographer.

14
15 9 *Patients:*

16
17 10 72 patients (median age 36 years, 19 males) receiving cabergoline for hyperprolactinaemia and 72 controls
18
19 11 prospectively matched for age, sex and cardiovascular risk factors.

20
21 12 *Measurements:*

22
23 13 Assessment of valvular mobility, regurgitation and morphology.

24
25 14 *Results:*

26
27 15 Median cumulative dose exposure for cabergoline was 126 (58–258) mg and patients had received
28
29 16 cabergoline for 53 (26–96) months. The frequency of mild mitral regurgitation was identical (5/72, 7%) in
30
31 17 patient and control groups. Mild aortic regurgitation was not significantly different between groups (4/72
32
33 18 [controls] vs. 2/72 [patients], $p = 0.681$). There was only 1 case of tricuspid regurgitation, which was mild and
34
35 19 observed in a cabergoline-treated patient. Nodular thickening of the right coronary cusp, non coronary cusp or
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37 20 left coronary cusp of the aortic valve was observed at a similar frequency in both groups. There were no cases
38
39 21 of extensive thickening of any valvular leaflet.

40
41 22 *Conclusion:*

42
43 23 Our data demonstrates that there is no association between cabergoline treatment for hyperprolactinaemia and
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45 24 valvulopathy. This study therefore supports continued use of low-dose cabergoline for patients with
46
47 25 hyperprolactinaemia.

1 Introduction

2 The ergot-based dopamine receptor agonist cabergoline plays an important role in antiparkinsonian therapy.
3 An association between cabergoline and the development of valvular heart disease (VHD) has been described,
4 limiting its use in Parkinson's disease.^{1,2,3} The pathophysiology of dopamine agonist-induced valvulopathy
5 has not been fully elucidated, but is thought to reflect agonist activity at the serotonin subtype 2B (5-HT_{2B})
6 receptor, causing inappropriate proliferation of valvular endothelial cells.⁴ Cabergoline has been used for the
7 last 15 years to treat hyperprolactinaemia and is the first-line dopamine agonist treatment for prolactinomas.
8 Nine studies to date have examined the frequency of VHD in patients receiving cabergoline for
9 hyperprolactinaemia.⁵⁻¹³ Only two of these studies describe an association with mild¹¹ or moderate¹² tricuspid
10 regurgitation. The remaining studies do not show any association between cabergoline treatment for
11 hyperprolactinaemia and VHD. However, these studies are frequently limited by control groups not
12 prospectively matched to the study population and assessment of only valvular regurgitation and not
13 morphology.

14

15 Following a review of clinical evidence relating to the risks of VHD associated with ergot-derived dopamine
16 agonist treatment, the European Medicines Agency (EMA) and the UK Medicines and Healthcare products
17 Regulatory Agency (MHRA) have issued recommendations for monitoring patients receiving cabergoline for
18 hyperprolactinaemia.^{14, 15} These stipulate that patients should undergo a baseline echocardiogram before
19 commencing treatment, a follow-up echocardiogram at 3-6 months following treatment initiation and
20 subsequently have an echocardiogram at 6-12 month intervals thereafter. These precautionary policies carry
21 significant implications for hospital services and health care costs. Based on the current estimated prevalence
22 of prolactinoma, this would result in approximately 1 218 000 extra echocardiograms performed in Europe
23 per annum if these policies were consistently implemented.¹⁶ Furthermore, mild mitral and aortic
24 regurgitation are not uncommon in the general population.¹⁷ Therefore, an unselected approach to
25 echocardiographic screening will inevitably produce false positive results, engendering patient anxiety and
26 resulting in additional costs in terms of the echocardiogram itself, follow-up, and further investigations.

1 1 Establishing whether there is a clinically significant association between cabergoline at the cumulative doses
2
3
4 2 used to treat hyperprolactinaemia and the development of VHD is therefore clearly important.^{18,19}
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6 3
7

8 4 In order to address this issue, we performed a cross-sectional echocardiographic study in patients with
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10 5 hyperprolactinaemia treated with cabergoline and in a control group matched for age, sex and cardiovascular
11
12 6 risk factors that had never received cabergoline. Our study was performed using a single *sonographer*,
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14 7 prospectively matched controls, and assessment of both valvular regurgitation and morphology *by two*
15
16 8 *independent echocardiographers*.
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1 **Methods**

2 **Subjects**

3 All study participants gave written informed consent and the study was approved by local research ethics
4 committees at each of the participating centres. Patients receiving cabergoline for hyperprolactinaemia were
5 identified following attendance at local endocrine clinics by participating endocrinologists (TT, WSD, KB,
6 KM, SR, NMM). To be eligible, patients must have received 0.5 mg cabergoline/week *or more* for at least 12
7 months. Patients with pituitary tumors co-secreting excess growth hormone and prolactin were excluded due
8 to the confounding effects of growth hormone on cardiac function. The total cumulative dose of cabergoline
9 for each patient was carefully calculated using their medical records. The use of any other dopamine agonists
10 prior to cabergoline treatment was recorded. The control group consisted of volunteers recruited by
11 advertisement. Controls were sex and age-matched. The two groups were carefully matched for coronary risk
12 factors (diabetes, smoking and hypertension, *although a lipid profile was not measured in either group*).
13 Exclusion criteria for both groups were: previous history of VHD, ischaemic heart disease, carcinoid
14 syndrome or connective tissue disease, previous use of ergotamine, methysergide, fenfluramine or
15 dexfenfluramine. Prior to echocardiography, resting blood pressure was recorded and a blood sample taken
16 for measurement of serum prolactin.

18 **Prolactin assay and normal ranges**

19 Serum prolactin was measured using an automated, two step, microparticle immunoassay employing a
20 chemiluminescent endpoint and magnetic separation (Architect, Abbott Diagnostics, Maidenhead, UK). The
21 interassay co-efficients of variation were 2.7%–4.4%. The detection limit of the assay is <13 mIU/L. Normal
22 values for basal prolactin are 75–375 mIU/L for males and 120–625 mIU/L for females.

24 **Echocardiographic measurements**

25 All echocardiography studies were performed *at Hammersmith Hospital* by the same experienced
26 sonographer (IZC), with the subjects in the left lateral decubitus position, using a Philips iE33 system (Philips
27 Medical Systems, Bothell, WA, USA), equipped with a phased-array transducer (5 to 1 MHz). An

1 electrocardiogram was simultaneously recorded from all subjects. Images were recorded and stored on a
2 digital format for subsequent off-line review and frame-by-frame analysis in a core lab (Hammersmith
3 Hospital). ProSolv CardioVascular Analyzer *software version 3.5* (Mount International Ultrasound Services
4 Ltd, The Glenmore Centre, Gloucester, UK) was used for *storage, reporting*, frame-by-frame analysis and
5 quantification of the lesions.

6
7 Two-dimensional echocardiographic examination and colour Doppler data was performed according to the
8 recommendations of the American Society of Echocardiography^{20, 21} and the European Association of
9 Echocardiography,²² using a standardised protocol. Each study was *read twice*, first by the operator (IZC)
10 who was unaware of the study status (patient *vs.* control) before sending it digitally to the core lab where it
11 was read by a *second* independent experienced reader also blinded to the study status of each participant (PN).

12
13 The following echocardiographic parameters were assessed: left ventricular (LV) end-systolic and end-
14 diastolic diameters, LV wall thickness, LV fractional shortening, left atrial diameter, right ventricular function
15 (eyeball estimation) regional wall motion abnormalities and LV ejection fraction. Pulsed Doppler of trans-
16 mitral flow was recorded from the apical four chamber view, with the Doppler sample volume being placed at
17 the level of the mitral valve leaflet tips in order to measure peak early (*E*) wave and atrial contraction (*A*) wave
18 velocities and early filling deceleration time (DT). Isovolumic relaxation time (IVRT) was measured by
19 placing the Doppler sample volume at the LV outflow tract. When necessary, pulmonary venous flow was
20 recorded. In order to classify the various patterns for left ventricle filling we used previously published
21 criteria²³ and divided the patients into four groups: Group 0 = normal filling pattern, Group 1 = abnormal
22 relaxation, Group 2 = pseudonormal flow pattern, and Group 3 = restrictive flow pattern.

23
24 The valvular assessment included the evaluation of morphology and function of the mitral, aortic, pulmonary
25 and tricuspid valves in multiple views following the recommendations of the European Society of
26 Echocardiography/American Society of Echocardiography.^{24,25} Colour Doppler echocardiography was
27 performed in all views after optimising gain and Nyquist limit. Standard continuous-wave and pulsed wave

1 Doppler examinations were performed. Leaflet mobility and thickness, chordae thickness and annular
2 calcification/thickening were analysed. Valvular regurgitation was graded as absent/trace (grade 0), mild
3 (grade 1), moderate (grade 2) or severe (grade 3) using multiple parameters. It is common that tricuspid and
4 pulmonary valves have a trace of regurgitation, which is considered physiological (grade 0). *Significant*
5 *valvular disease was considered to be moderate or severe valvular regurgitation. Mild mitral regurgitation*
6 *accompanied by prolapse was also considered to be significant.*

7
8 Continuous-wave Doppler sampling of the peak tricuspid regurgitant jet velocity was used to estimate the
9 right-ventricular-to-right-atrial systolic pressure gradient with the use of the modified Bernoulli equation
10 ($4 \times [\text{tricuspid regurgitant velocity}]^2$). The mean right atrial pressure was calculated according to the degree of
11 collapse of the inferior vena cava with inspiration.

12 13 **Statistical Analysis**

14 Statistical analysis was performed using SPSS Version 16.0 for Windows (SPSS Inc., Chicago, IL, USA).
15 Continuous variables were compared between two groups using the Mann-Whitney U test and values are
16 reported as median and interquartile range. The relationship between two categorical variables was analysed
17 using the two-sided Fisher's exact test. A *p* value of <0.05 was conventionally considered to be statistically
18 significant.

1 Results

2 *Clinical characteristics of control and study populations*

3 The study population consisted of 72 controls and 72 patients who received cabergoline. The clinical
4 characteristics of each group are summarised in Table 1, which confirms matching of the control group
5 according to age, sex and presence of coronary risk factors. As expected, despite cabergoline treatment, serum
6 prolactin was significantly higher in the cabergoline-treated group compared to controls: 239 (174–290)
7 [controls] vs. 419 (90–684) mIU/L [cabergoline group], $p = 0.021$. Causes of hyperprolactinaemia in the
8 patient group receiving cabergoline were: 28 macroprolactinomas (>1 cm diameter), 40 microprolactinomas
9 (<1 cm diameter), 2 due to disconnection hyperprolactinaemia (pituitary stalk compression), and 2 with
10 hyperprolactinaemia without any obvious pituitary lesion. *Nine patients required pituitary hormone*
11 *replacement*. Cumulative dose exposure to cabergoline was 126 (58–258) mg and patients had received
12 cabergoline treatment for 53 (26–96) months.

14 *Valvular mobility and morphology*

15 These data are described in Table 2 (mitral and aortic valves) and Table 3 (tricuspid and pulmonary valves).
16 *There was no significant difference in observed abnormalities of valvular mobility or morphology when*
17 *comparing cabergoline-treated patients with controls. In the four cases of anterior mitral valve leaflet*
18 *prolapse (all cabergoline-treated patients), one of these also had evidence of mild mitral valve regurgitation.*
19 *Of the six subjects with posterior mitral valve leaflet prolapse, mild mitral valve regurgitation was also*
20 *present in three out of the five control subjects and in the cabergoline-treated patient.* There were 24/144
21 (17%) cases where there was inter-observer variability in valvular assessment between the two
22 echocardiographers. *As specified in the study protocol at the onset of the study, these cases were individually*
23 *reviewed by the more experienced echocardiographer (PN), who remained blinded to the treatment status of*
24 *these individuals, and a consensus was reached. The frequency of mild mitral regurgitation was identical*
25 *(5/72) when comparing both groups. Mild aortic regurgitation was observed in 2/72 cabergoline-treated*
26 *patients compared to 4/72 controls. There was no significant difference in the observed frequency of nodular*
27 *thickening of the right coronary cusp, non-coronary cusp or left coronary cusp of the aortic valve when*

1 comparing patients and controls. No participants (controls or cabergoline-treated patients) had extensive
2 thickening of any valvular leaflet. Only one study participant, a cabergoline-treated patient, had mild tricuspid
3 regurgitation. The prevalence of mild valvular regurgitation in cabergoline-treated patients was too low to
4 perform a correlation with cumulative cabergoline dose exposure.

5
6 Twenty-seven (38%) of the cabergoline-treated patient group had previously been treated with bromocriptine
7 prior to cabergoline treatment. Only one of the five patients with mild mitral regurgitation and one of the two
8 patients with mild aortic regurgitation had previously received bromocriptine. The patient with mild tricuspid
9 regurgitation had never received bromocriptine treatment.

10 11 *Left ventricular function*

12 Left ventricular ejection fraction (LVEF) was similar between both groups (LVEF: 65 (60–69) [controls] vs.
13 64 (60–68) % [cabergoline group], $p = 0.273$). There was no significant difference in the prevalence of
14 diastolic dysfunction between both groups (diastolic dysfunction: 11/72 (15 %) [controls] vs. 9/72 (13 %) [cabergoline group], $p = 0.810$).

15 16 17 *Right ventricular systolic pressure*

18 Estimated right ventricular systolic pressure (RSVP) was measurable in 35/72 (49%) control subjects and
19 45/72 (63%) patients receiving cabergoline. This did not differ significantly between the two groups (RSVP:
20 23 (18–26) [controls] vs. 20 (18–26) mmHg [cabergoline group], $p = 0.287$).

1 Discussion

2 Patients with hyperprolactinaemia require lower doses of cabergoline (typically 0.5–1 mg twice weekly),
3 compared with 2–6 mg daily in Parkinson's disease.¹⁸ Zanettini *et al* described restrictive valvulopathy in
4 Parkinson's patients receiving a cumulative cabergoline dose twenty times higher than that reported in the
5 current study.³ In our study, *albeit with smaller patient numbers*, cabergoline treatment of
6 hyperprolactinaemia at a median dose of 126 mg and median duration of 53 months is not associated with
7 valvular regurgitation or morphological valve abnormalities. This may reflect the lower cumulative doses of
8 cabergoline used in the treatment of hyperprolactinaemia compared to those used to treat Parkinson's disease.
9 The prevalence of mild aortic or mitral regurgitation in the control group of our study (6–7%) is similar to that
10 described in the Framingham Heart Study.¹⁷ Trace tricuspid or pulmonary regurgitation was observed in all of
11 our patients and controls. This was not reported as valvular regurgitation since it is considered
12 physiological.²⁶ Only one subject, a cabergoline-treated patient, had mild tricuspid regurgitation.
13
14 Consistent with our findings, most studies to date do not support an association between the use of
15 cabergoline treatment of hyperprolactinaemia and clinically significant VHD.^{5-10, 13} The cumulative
16 cabergoline dose exposure in the current study is similar to the doses described in most of these studies.^{5-7, 10,}
17 ¹¹ It is important to note that one of these studies did not have a control group in its study design ¹³ and only
18 three studies used a prospectively matched control group for comparison.^{5, 6, 12} Only two previous studies have
19 used a single blinded echocardiographer.^{6, 11} We chose to minimise observer error, which can be a significant
20 variable when making echocardiographic measurements,²⁷ by using a single operator for all
21 echocardiographic studies and two independent experienced echocardiographers for study interpretation.
22 Detailed assessment of morphological valve abnormalities, which may reflect early restrictive valvulopathy,
23 is limited to two previous studies, both of which describe a non-significant increase in mitral valve leaflet
24 thickening in cabergoline treated patients.^{5, 11} Our data does not demonstrate any increase in valvular leaflet
25 thickening with cabergoline treatment. Therefore, the strengths of the current study are the use of a single,
26 blinded *sonographer*, a control group carefully matched for age, sex and cardiovascular risk factors, and the

1 assessment by two independent and accredited echocardiographers of both valvular morphology and
2 regurgitation.
3

4 One recent cross-sectional study demonstrated a significant association between cabergoline treatment of
5 hyperprolactinaemia and moderate tricuspid regurgitation, but not with mild tricuspid regurgitation.¹² This
6 unusual finding is not consistent with a simple dose-response relationship. Kars *et al* described increased mild
7 tricuspid regurgitation in patients receiving cabergoline for hyperprolactinaemia compared to controls.¹¹
8 *Notably, their control group, selected from an echocardiographic database, had been referred for*
9 *investigation of atypical chest pain, palpitations or syncope without murmur. This may explain the much*
10 *higher frequency of mild mitral regurgitation (22%) observed in their control population compared to the*
11 *current study and described by others.¹⁷ Conversely, our matched controls were prospectively recruited by*
12 *advertisement. This method of recruitment may also be associated with selection bias. However, this will be*
13 *significantly less compared to recruitment of controls from an echocardiographic database, which could*
14 *result in bias from potential underlying cardiac disease.* Although our patients received cabergoline over a
15 similar duration to both these studies, the median cumulative cabergoline dose exposure was lower in our
16 study, which is another possibility for this difference in observations.^{11, 12}

17
18 Van Camp *et al* were the first to describe an association between dopamine agonists and VHD, describing
19 restrictive valvulopathy in patients receiving pergolide for Parkinson's disease.²⁸ This group described a
20 significant increase in mitral valve tenting in the pergolide-treated group compared to controls, a finding
21 suggestive of a reduced compliance of the mitral valve leaflets and therefore the development of fibrosis.
22 Subsequently, one of the earliest studies to describe a similar association between cabergoline treatment of
23 Parkinson's disease and VHD also reported an association between cumulative cabergoline dose and mitral
24 valve tenting.³ Two of the recent studies of the effects of cabergoline treatment for hyperprolactinaemia on
25 valvular dysfunction have described an association with mitral valve tenting.^{5, 9} There are several issues
26 regarding the assessment of mitral valve tenting. Firstly, the assessment is limited using trans-thoracic
27 echocardiography and the measurement of this parameter depends critically on the operator and the technique

1 of scanning, particularly as 2-D echocardiography may not give an adequate appraisal of the 3-D shape of the
2 mitral valve and its dynamics during systole.²⁹ Trans-oesophageal echocardiography may be a better
3 modality to assess mitral valve tenting, preferably with the addition of real-time three-dimensional imaging.
4 Secondly, mitral valve tenting was validated for assessment of ischaemic mitral valve disease related to left
5 ventricular wall motion abnormality rather than dopamine-agonist induced mitral valvulopathy where left
6 ventricular systolic function is normal. Thirdly, assessment of mitral valve tenting is not a feature of the
7 current European or American Echocardiography guidelines.²² Therefore, we questioned the ability and the
8 validity of assessing mitral valve tenting with trans-thoracic two-dimensional echocardiography, and *this was*
9 *not a pre-specified* parameter in the current study. *Nevertheless, we have not observed any mitral valve*
10 *tenting in the current study despite careful segmental valve description.*

11
12 In light of the current evidence, which does not support a clear association between cabergoline treatment of
13 hyperprolactinaemia and VHD, a sensible balance between costly investigations versus patient safety is
14 required. We therefore suggest the following recommendations:

- 15 1. Minimisation of cumulative dose exposure to cabergoline: cabergoline withdrawal has been advocated in
16 patients with tumoral and non-tumoral hyperprolactinaemia in whom serum prolactin has normalised with
17 sufficient tumor shrinkage on MRI.³⁰ Therefore, it may be useful to schedule strategic treatment interruptions
18 every two years in appropriate patients and to stop cabergoline in the long-term if serum prolactin remains
19 normal following cabergoline withdrawal.
- 20 2. A targeted approach to echocardiographic screening: A recent nested case-control study of patients
21 receiving dopamine agonists for Parkinson's disease has identified several independent risk factors for the
22 development of aortic and mitral valve disease, including the presence of hypertension, age over 70 years and
23 a mean daily dose of cabergoline of 0.3–1.2 mg.³¹ Therefore, rather than following an unselected, frequent
24 echocardiographic screening approach towards patients receiving cabergoline for hyperprolactinaemia,^{14,15}
25 which will sharply escalate the costs of care, we would recommend regular echocardiographic screening
26 every 6-12 months in individuals with hypertension and/or cumulative cabergoline dose exposure equivalent
27 to a weekly cabergoline dose of 2 mg or above. Although most patients receiving cabergoline for

1 hyperprolactinaemia are younger than those with Parkinson's disease, this frequency of echocardiographic
2 screening should also be recommended for patients over 70 years. Otherwise, a reduced frequency of
3 screening (e.g. every 12–18 months) is likely to be adequate.

4
5 In conclusion, the current study does not support an association between low-dose cabergoline treatment for
6 hyperprolactinaemia over several years and VHD. Longitudinal, prospective studies are now needed to clarify
7 the precise risks of VHD associated with low-dose cabergoline treatment for hyperprolactinaemia.

For Peer Review

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	Control group (n=72)	Cabergoline-treated group (n=72)	<i>P</i> value
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9	38 (31–49)	36 (30–45)	0.339
10			
11	20/52 (39)	19/53 (36)	0.852
12			
13	27 (24–31)	25 (22–29)	0.050
14			
15			
16	239 (174–290)	419 (90–684)	0.021
17			
18	120 (110–132)	119 (111–130)	0.849
19			
20	74 (69–80)	75 (68–81)	0.756
21			
22			
23	4/68 (6%)	7/65 (11%)	0.348
24			
25	3/69 (4%)	5/67 (7%)	0.468
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28	12/60 (20%)	13/59 (22%)	0.826
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Table 1. Characteristics of patients receiving cabergoline treatment for hyperprolactinaemia and controls.

Data for continuous variables are expressed as the median value (interquartile range in brackets) and for categorical variables, frequency (percentages in brackets). Reference ranges for serum prolactin: 75–375 mU/L (males), 125–625 mU/L (females). BMI = body mass index. BP = blood pressure.

Data were compared using a two sided Fisher's exact test (categorical variables) or Mann-Whitney U test (continuous variables).

	Control group (n=72)	Cabergoline group (n = 72)	<i>P</i> value
Mitral valve			
Anterior leaflet mobility			
Normal	72 (100%)	68 (94%)	0.120
Prolapsed	0 (0%)	4 (6%)	
Posterior leaflet mobility			
Normal	67 (93%)	71 (99%)	0.209
Prolapsed	5 (7%)	1 (1%)	
Mitral regurgitation			
None/trace	67 (93%)	67 (93%)	1.000
Mild	5 (7%)	5 (7%)	
Moderate	0 (0%)	0 (0%)	
Severe	0 (0%)	0 (0%)	
Anterior leaflet thickening			
Normal	69 (96%)	71 (99%)	0.620
Nodular thickening	3 (4%)	1 (1%)	
Posterior leaflet thickening			
Normal	72 (100%)	72 (100%)	1.000
Nodular thickening	0 (0%)	0 (0%)	
Chordae thickening			
Normal	72 (100%)	72 (100%)	1.000
Thickened	0 (0%)	0 (0%)	
Annular thickening/calcification			
None	71 (99%)	72 (100%)	1.000
Mild	1 (1%)	0 (0%)	
Aortic valve			
Aortic root			
Normal	72 (100%)	72 (100%)	1.000
Thickened	0 (0%)	0 (0%)	
Leaflet mobility			
Normal	72 (100%)	72 (100%)	1.000
Reduced	0 (0%)	0 (0%)	
RCC leaflet thickening			
Normal	70 (97%)	69 (96%)	1.000
Nodular	2 (3%)	3 (4%)	
NCC leaflet thickening			
Normal	68 (94%)	67 (93%)	1.000
Nodular	4 (6%)	5 (7%)	
LCC leaflet thickening			
Normal	71 (99%)	71 (99%)	1.000
Nodular	1 (1%)	1 (1%)	
Aortic regurgitation			
None/trace	68 (94%)	70 (97%)	0.681
Mild	4 (6%)	2 (3%)	
Moderate	0 (0%)	0 (0%)	
Severe	0 (0%)	0 (0%)	

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1 **Table 2. Mitral and aortic valvular abnormalities in controls compared to patients treated with**
2 **cabergoline.** RCC = right coronary cusp, LCC = left coronary cusp, NCC = non coronary cusp. Data
3 are frequency (percentage in brackets).

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	Control group (n=72)	Cabergoline group (n = 72)	P value
<u>Tricuspid valve</u>			
Leaflet mobility			
Normal	72 (100%)	72 (100%)	1.000
Reduced	0 (0%)	0 (0%)	
Leaflet thickening			
Normal	72 (100%)	72 (100%)	1.000
Thickened	0 (0%)	0 (0%)	
Tricuspid regurgitation			
None/trace	72 (100%)	71 (99%)	1.000
Mild	0 (0%)	1 (1%)	
Moderate	0 (0%)	0 (0%)	
Severe	0 (0%)	0 (0%)	
TR velocity (cm/s)	2.1 (1.8–2.2)	1.95 (1.75–2.2)	0.162
<u>Pulmonary valve</u>			
Leaflet mobility			
Normal	72 (100%)	72 (100%)	1.000
Reduced	0 (0%)	0 (0%)	
Leaflet thickening			
Normal	72 (100%)	72 (100%)	1.000
Thickened	0 (0%)	0 (0%)	
Pulmonary regurgitation			
None/trace	72 (100%)	72 (100%)	1.000
Mild	0 (0%)	0 (0%)	
Moderate	0 (0%)	0 (0%)	
Severe	0 (0%)	0 (0%)	

Table 3. Tricuspid and pulmonary valvular abnormalities in controls compared to patients receiving cabergoline. TR velocity = tricuspid regurgitation maximum velocity, recordable in 52

1 controls and 41 cabergoline-treated patients, expressed as median (interquartile range in brackets).
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3 Remaining data are frequency (percentage in brackets).
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