

CLINICAL STUDY

Safety of long-term treatment with cabergoline on cardiac valve disease in patients with prolactinomas

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Abstract

Objective: Cabergoline (CAB) has been found to be associated with increased risk of cardiac valve regurgitation in Parkinson's disease, whereas several retrospective analyses failed to detect a similar relation in hyperprolactinemic patients. The current study aimed at investigating cardiac valve disease before and after 24 and 60 months of continuous treatment with CAB only in patients with hyperprolactinemia.

Subjects and methods: Forty patients (11 men and 29 women, aged 38.7 ± 12.5 years) newly diagnosed with hyperprolactinemia entered the study. Cumulative CAB dose ranged from 12 to 588 mg (median 48 mg) at 24 months and 48–1260 mg (median 149 mg) at 60 months. All patients underwent a complete trans-thoracic echocardiographic examination. Valve regurgitation was assessed according to the American Society of Echocardiography.

Results: At baseline, the prevalence of trace mitral, aortic, pulmonic, and tricuspid regurgitations was 20, 2.5, 10, and 40% respectively, with no patient showing clinically relevant valvulopathy. After 24 months, no change in the prevalence of trace mitral ($P=0.78$) and pulmonic ($P=0.89$) regurgitations and of mild aortic ($P=0.89$) and tricuspid ($P=0.89$) regurgitations was found when compared with baseline. After 60 months, the prevalence of trace tricuspid regurgitation was only slightly increased when compared with that after 24 months (37.5%; $P=0.82$), but none of the patients developed significant valvulopathy. No correlation was found between cumulative dose and prevalence or grade of valve regurgitation at both evaluations. Prolactin levels normalized in all patients but one.

Conclusion: CAB does not increase the risk of significant cardiac valve regurgitation in prolactinomas after the first 5 years of treatment.

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Introduction

Dopamine agonists (DA) are first-line treatment for patients with both prolactinomas (1, 2) and Parkinson's disease (PD) (3). In recent years, there has been an increasing recognition that ergot-derived DA, such as pergolide and cabergoline (CAB), are associated with an increased risk of cardiac valve disease in 29–39% of patients with PD (4, 5, 6), usually treated with mean weekly doses up to 25 mg (7) and taking median cumulative doses ranging from 2600 to 6700 mg (8), with the risk of valvular disease being significantly related to cumulative dose and treatment duration. Particularly, restrictive valvulopathy has been found in 33% of patients with PD receiving pergolide therapy, but in none of those never treated with DA (4). A few years later, the increased risk of newly diagnosed moderate-to-severe valvular regurgitation has been confirmed in patients with PD treated with pergolide or CAB

when compared with those receiving different anti-Parkinsonian medications (5, 6). Consequently, in 2007, pergolide has been withdrawn from the US market (9). More recently, in a review of all reports on fibrotic reactions associated with the administration of DA, the US Adverse Event Reporting System database identified 159 cases of clinically relevant valvulopathy in treated patients and 57% of them were taking CAB (10). Albeit no clear distinction was made between patients with PD and those with hyperprolactinemia, the authors emphasized that the risk of relevant valvulopathy was significantly dose dependent (10). Moreover, use of DA in patients with PD has been shown to be not associated with an increased risk of newly diagnosed heart failure (11).

Whether treatment with CAB is associated with an increased risk of clinically significant valvulopathy in patients with prolactinomas is still a matter of debate. A recent nested case–control study (12) has shown in a

large series that treatment with DA is associated with an increased risk of clinically relevant valve disease (CRVD) in PD but not in hyperprolactinemic patients. Over the past 5 years, 15 independent studies (13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27) (Table 1) have investigated the effects of CAB on the development of CRVD in patients with prolactinomas. Overall, these studies have reported a median CRVD rate of ~4%, with the prevalence of CRVD ranging from 54% (13), 40% (24), 15% (17) to 0% (15, 16, 19, 21) and valvulopathy being assessed according to the International Guidelines suggested by the American Society of Echocardiography (28, 29) in all studies and also according to the European Association of Echocardiography (30, 31) in ten studies (13, 16, 17, 18, 20, 22, 23, 25, 26, 27). Moreover, a significant correlation between cumulative dose of CAB and prevalence of valve disease has been demonstrated in only two reports (13, 24), whereas the vast majority of studies have agreed on safety of treatment with CAB on valvulopathy in hyperprolactinemic patients. However, all previous studies are observational and retrospective; prospective studies are still lacking and few data are nowadays available on the effects of CAB on new-onset relevant valvulopathy in patients with prolactinomas after long-term treatment. The current study aimed at investigating the prevalence and severity of valve regurgitation in patients with prolactinomas before and after 24 and 60 months of continuous treatment with CAB only.

Subjects and methods

Inclusion and exclusion criteria

This prospective study included patients >18 years old with a newly established diagnosis of hyperprolactinemia starting treatment with CAB, after the written informed consent with respect to confidentiality statement of data

collection according to the Italian privacy policy had been obtained. Exclusion criteria included: i) history of cardiac valve abnormalities, calcifications, or regurgitations associated with annular dilatation or excessive leaflet motion; ii) mitral regurgitation associated with left ventricular all-motion abnormalities or left ventricular dilatation; iii) autoimmune diseases associated with hyperprolactinemia; iv) suspicion of drug or alcohol abuse; v) treatment duration shorter than 12 months; vi) CAB withdrawal for longer than 1 month; vii) pregnancy occurring while on treatment with CAB; viii) use of DA different from CAB; and ix) denied consent with respect to confidentiality statement of data collection according to the Italian privacy policy.

Patients

Sixty-nine newly diagnosed consecutive patients with hyperprolactinemia attended the outpatient clinic of Neuroendocrine Disease Unit at 'Federico II' University of Naples between January 1st 2007 and December 31st 2007, with the last patient being recruited on November 29th 2007. Pituitary imaging revealed a microadenoma in 34 patients, a macroadenoma in 27 patients, and non-tumoral hyperprolactinemia in eight patients. Twenty-nine patients were excluded from the analysis because of gestation occurring while on CAB treatment and requiring therapy discontinuation after a follow-up period shorter than 6 months in eight patients (11.6%, all with non-tumoral hyperprolactinemia), treatment duration shorter than 12 months in 13 patients (18.8%) because of treatment resistance requiring surgery, autoimmune disease in six patients (8.7%), and withdrawal of treatment longer than 1 month in two patients (2.9%). Therefore, for the purpose of the study, 40 patients (11 men and 29 women, 18 with microadenoma and 22 with macroadenoma), aged 38.7 ± 12.5 years, entered the current study. Based on power calculation and sample size

Table 1 Effects of treatment with cabergoline on valvular heart disease in patients with pituitary tumors: overview of the literature.

Reference no.	Patient no.	Age (years)	CD (mg)	TD (months)	CRVD (%)	Valve	Relation with CD
(18)	102	51 ± 14	18–1718	12–228	2	Mitral (thickening)	No
(15)	45	41 ± 10	146 ± 220	39 ± 29	0	–	No
(17)	47	47 ± 1	363 ± 65	62 ± 5	15 (grade 3), 2 (grade 4)	Tricuspid and aortic	No
(13)	50	36 ± 10	414 ± 390	16–250	54	Tricuspid	Yes
(16)	44	42 ± 13	311	44.8	0	–	No
(14)	100	41 ± 13	279 ± 301	67 ± 39	7	–	No
(20)	50	51 ± 2	443 ± 53	12–156	0	–	No
(19)	70	44	282 ± 271	55 ± 22	5.7	–	No
(21)	100	44 ± 13	253 ± 52	48 ± 4	0	–	No
(22)	72	38 (31–49)	126	53	2.7	Aortic	No
(26)	51	42 ± 13	238.7 ± 242	12–52	3.9	Aortic	No
(23)	45	48 ± 1.8	401 ± 55	24	5	Mitral and tricuspid	No
(25)	103	38 ± 10	174	46 ± 28	2	Aortic	No
(24)	62	37 ± 10.6	216.2 ± 306	51 ± 42	40	Tricuspid	Yes
(27)	32	39 ± 10	158	30–96	6.2	Tricuspid and aortic	No

CD, cumulative dose; TD, treatment duration; CRVD, clinically relevant valve disease.

analysis, a total of 19 patients were required for a statistical power of 80% at 5% significance set. The patients' profiles at study entry is shown in Table 2.

Study protocol

The present study is prospective in nature. At diagnosis and thereafter at 3- to 6-month intervals as per routine clinical practice, all patients were admitted to the hospital for a complete endocrine screening and physical examination. Once a year, a cardiological visit, an electrocardiography, and an echocardiography were performed. At each clinical examination, blood pressure was measured in the right arm, with the subjects in a relaxed sitting position for 5 min using a standard mercury sphygmomanometer. Three measurements were taken and averaged to give blood pressure values used in this analysis. If present, systemic arterial hypertension was classified as mild (stage 1) when the systolic and diastolic blood pressure was between 140 and 159 mmHg and between 90 and 99 mmHg respectively; severe (stage 2) when the systolic and diastolic blood pressure was >160 and >100 mmHg respectively; and pre-hypertension was defined as systolic blood pressure between 120 and 139 and diastolic blood pressure between 80 and 89 mmHg (32). Heart rate was also measured. Serum PRL was assessed in all patients at diagnosis and every 3–6 months thereafter, according to our treatment protocol. This study considered three time points: the baseline, the 24-month, and the 60-month evaluation.

Treatment protocol

According to our previous studies (1, 2, 13, 33, 34, 35, 36, 37, 38), in patients with microprolactinoma and in those with non-tumoral hyperprolactinemia, CAB therapy was administered orally at a starting dose of 0.25 mg twice weekly for the first 2 weeks and then 0.5 mg twice weekly. Dose adjustment was carried out every 3–6 months during our follow-up on the basis of PRL levels. In patients with macroprolactinoma, starting dose was 0.25 mg once a week for the first week and then twice weekly. Dose adjustment was performed at 3- to 6-month intervals as for patients with microprolactinoma or non-tumoral hyperprolactinemia. In patients who did not have normalized PRL levels, CAB dose was progressively

increased up to 5 mg/week. In patients achieving PRL levels <5 µg/l (the lower limit of normality), CAB dose was reduced to maintain PRL levels in the normal range. Thus, final CAB dose ranged from 0.25 to 5 mg/week. In order to elucidate the role of CAB dose and duration on echocardiographic findings, the cumulative dose for individual patients was calculated. As doses changed throughout the follow-up, the cumulative dose was the sum of each dose used multiplied for the months of treatment in which that dose was employed. CAB cumulative dose ranged from 12 to 588 mg (median 48 mg) after 24-month therapy and from 48 to 1260 mg (median 149 mg) after 60-month follow-up. In order to correlate the rate of valvulopathy with treatment schedule at both evaluations, tertiles of CAB dose were also calculated and resulted as follows: <0.5 mg/week = tertile 1, 0.51–1.124 mg/week = tertile 2, and >1.125 mg/week = tertile 3 at 2-year follow-up; <0.9 mg/week = tertile 1, 0.91–2.55 mg/week = tertile 2 and >2.56 mg/week = tertile 3 at 5-year follow-up.

Echocardiographic study

At study entry and thereafter once a year, all patients underwent a complete trans-thoracic echocardiographic examination. Echocardiographic examinations were performed in all patients by two experienced cardiologists, blinded to the study participant's data in order to limit any operator bias (39). Both cardiologists worked on the same machine; therefore, technical sensitivity was always identical throughout the study. Standardized operating procedures were used based on international guidelines (40) and monthly meetings were conducted for quality control. The echocardiographic quantitative assessment was performed according to standard methods (41). Recording and measurements of Doppler-derived diastolic function were performed according to the recommendations of the American Society of Echocardiography (28). Pulmonary systolic arterial pressure was estimated by continuous wave Doppler as peak regurgitation velocity plus an assumed right atrial pressure in relation to the size and respiratory excursion of inferior cava vein visualized in subcostal view (42). A cut-off point value of pulmonary arterial systolic pressure of more than 25 mmHg was considered as diagnostic for arterial pulmonary hypertension. Quantification of valvular regurgitation was made according to the recommendations of the American Society of Echocardiography (29). Valve regurgitations were defined and categorized as absent = grade 0, trace = grade 1, mild = grade 2, moderate = grade 3, and severe = grade 4. Clinically relevant valve regurgitations were diagnosed when grading was ≥3 for mitral and tricuspid valve and ≥2 for aortic and pulmonic valve (29).

Hormonal assays

PRL levels were measured by chemiluminescent immunometric assay using commercially available kits

Table 2 Patients' profiles at study entry.

Patient (n)	40
Patients' age (years)	38.7 ± 12.5
M/F	11/29
Microadenoma no. (%)	18 (45)
Macroadenoma no. (%)	22 (55)
Baseline PRL levels (µg/l)	789.3 ± 239.3
CAB starting dose (mg/week)	0.25–0.5

(Immulite, DPC, Llambris, UK). The sensitivity was 0.16 µg/l; the intra-assay coefficients of variation for PRL concentrations of 22 and 164 ng/ml were 2.3 and 3.8% respectively; and the corresponding inter-assay coefficients of variation were 6%. Hyperprolactinemia was defined as a serum PRL level of >25 µg/l on two different samples more than 1 week apart.

Statistical analysis

Data were analyzed using SPSS Software for Windows, version 19.0 (SPSS, Inc. package). Data are reported as mean ± s.d., unless otherwise specified. The comparison between the numerical data before and after treatment with CAB was made by non-parametric Wilcoxon test. The comparison between prevalence was performed by χ^2 test corrected by Fisher exact test when necessary. The correlation study was done by calculating the Pearson's correlation coefficients. Significance was set at 5%.

Results

The results of the current study are shown in Table 3.

Baseline

In our patient cohort, baseline PRL levels were 789.3 ± 239.3 µg/l. The prevalence of mitral, aortic, pulmonic, and tricuspid valve regurgitations was 20, 2.5, 10, and

40% respectively (Fig. 1). Among patients, none had CRVD at study entry. Grading is detailed in Table 3.

24-Month evaluation

At a median cumulative dose of 48 mg (range: 12–588 mg), PRL levels were significantly reduced by 94% as overall ($P=0.003$, Table 3) compared with baseline evaluation and resulted fully normalized in all patients but one. No patient developed moderate or severe valve insufficiency, and none had arterial pulmonary hypertension. When compared with baseline, a slight but not significant increase was found in the prevalence of trace mitral (17.5 vs 22.5%, $P=0.78$) and pulmonic (10 vs 12.5%, $P=0.89$) valve regurgitations and of mild tricuspid (5 vs 7.5%, $P=0.89$) and aortic (0 vs 2.5%, $P=0.89$) valve regurgitations, with the latter being found only in one hypopituitary male patient affected with arterial hypertension and with evidence of new-onset aortic root dilatation and fibrosis at the echocardiographic examination. According to dose tertiles, 20 patients (50%) were in the first tertile, ten (25%) in the second tertile, and ten (25%) in the third tertile. Mitral and pulmonic valve insufficiency occurred in 60 and 40% of patients in the second tertile and in 40% ($P=0.6$) and 10% ($P=0.3$) of those in the third tertile respectively. Similarly, tricuspid valve regurgitation was recorded in 35% of patients in the first tertile, 60% ($P=0.36$) in the second tertile, and 40% ($P=0.89$) in the third tertile.

Table 3 Effects of treatment with CAB on disease control and on development of clinically relevant valve disease in our patient cohort.

	Baseline (A)	24 Months (B)	60 Months (C)	P (A vs B)	P (B vs C)	P (A vs C)
PRL levels (µg/l)	789.3±239.3	13.6±22.4	3.4±6.5	0.003	0.003	<0.001
CAB cumulative dose/mg (range)	–	48 (12–588)	149 (48–1260)	–	–	–
Mitral valve regurgitation (%)						
Total	20	25	25	0.79	1	0.79
Trace	17.5	22.5	22.5	0.78	1	0.78
Mild	2.5	2.5	2.5	1	1	1
Moderate	0	0	0	–	–	–
Severe	0	0	0	–	–	–
Aortic valve regurgitation (%)						
Total	2.5	5	5	0.92	1	0.92
Trace	2.5	2.5	2.5	1	1	1
Mild	0	2.5	2.5	0.89	1	0.89
Moderate	0	0	0	–	–	–
Severe	0	0	0	–	–	–
Pulmonic valve regurgitation (%)						
Total	10	12.5	12.5	0.89	1	0.89
Trace	10	12.5	12.5	0.89	1	0.89
Mild	0	0	0	–	–	–
Moderate	0	0	0	–	–	–
Severe	0	0	0	–	–	–
Tricuspid valve regurgitation (%)						
Total	40	42.5	45	0.89	0.82	0.78
Trace	35	35	37.5	1	0.89	0.89
Mild	5	7.5	7.5	0.89	1	0.89
Moderate	0	0	0	–	–	–
Severe	0	0	0	–	–	–

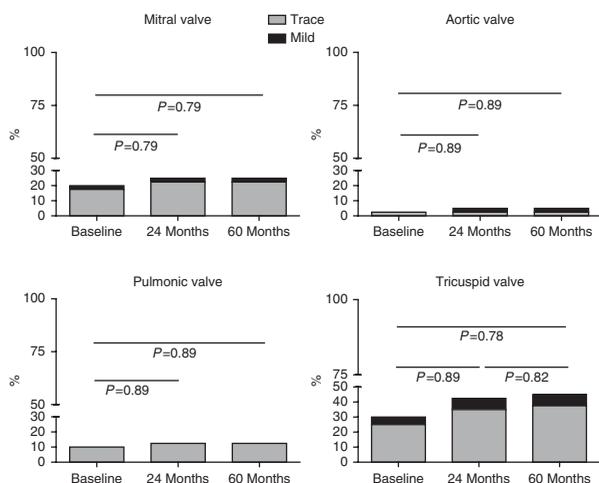


Figure 1 Prevalence and severity of cardiac valve regurgitations in the present series of prolactinomas at baseline and after 24 and 60 months of treatment with CAB. A slight but not significant increase was found in both rate and grading of valve insufficiency after 2 and 5 years of therapy with CAB. Mild aortic insufficiency occurred in only one patient (2%) after 24 months of treatment, whereas moderate or severe mitral, tricuspid, and pulmonic regurgitations did not occur in the current patient cohort after 24 or 60 months of follow-up.

60-Month evaluation

At a median cumulative dose of 149 mg (range: 48–1260 mg), PRL levels were significantly lower than 24-month evaluation by 75% ($P=0.003$, Table 3), with complete normalization in all patients but one. As at 24-month evaluation, among patients none developed moderate or severe valve insufficiency, and none showed arterial pulmonary hypertension. As shown in Table 3, after 60 months of treatment, only the prevalence of tricuspid valve regurgitation was found further slightly but not significantly increased compared with 24 months (42.5 vs 45%, $P=0.82$) and baseline (40 vs 45%, $P=0.78$), with trace tricuspid valve regurgitation being 37.5% ($P=0.89$). No further impairment of both aortic root dilatation and fibrosis or aortic regurgitation was observed in the hypopituitary male with severe arterial hypertension who continued CAB therapy. According to dose tertiles, 24 patients (60%) were in the first tertile, nine (22.5%) in the second tertile, and seven (17.5%) in the third tertile. Mitral valve insufficiency occurred in 25% of patients in the first tertile, 22% ($P=0.78$) of those in the second tertile, and 28.6% ($P=0.76$) in the third tertile. Similarly, tricuspid valve regurgitation was recorded in 29% of patients in the first tertile, 66% ($P=0.12$) in the second tertile, and in 71% ($P=0.11$) in the third tertile. Pulmonic insufficiency was found in 44% of patients in the second tertile and 11% ($P=0.37$) in the third tertile. Compared with short-term evaluation, prevalence of each valve insufficiency did not significantly change

after long-term treatment with CAB (Fig. 2). Particularly, a slight but not significant increase was found in the prevalence of mitral regurgitation (0 vs 25%, $P=0.27$) in tertile 1, pulmonic (40 vs 44%, $P=0.72$) and tricuspid (60 vs 66%, $P=0.84$) regurgitations in tertile 2, and tricuspid regurgitation (40 vs 71%, $P=0.47$) in tertile 3 (Fig. 2). Prevalence of tricuspid regurgitation in tertile 1 (35 vs 29%, $P=0.92$) and of mitral regurgitation in tertile 2 (60 vs 22%, $P=0.23$) and in tertile 3 (40 vs 28.6%, $P=0.9$) were found even slightly reduced after 60-month CAB when compared with short-term evaluation (Fig. 2).

Correlation study

After 24 months of treatment with CAB, no significant correlation was found between either median cumulative dose and prevalence of mitral ($r=-0.19$, $P=0.26$), aortic ($r=-0.15$, $P=0.38$), pulmonic ($r=-0.10$, $P=0.55$), and tricuspid ($r=-0.18$, $P=0.29$) valve or grading of mitral ($r=-0.19$, $P=0.26$), aortic ($r=-0.14$, $P=0.40$), pulmonic ($r=-0.08$, $P=0.60$), and tricuspid ($r=-0.09$, $P=0.59$) valve insufficiency. Similarly, at 60-month follow-up, no significant correlation was found between either median cumulative dose and prevalence of mitral ($r=-0.18$, $P=0.29$), aortic ($r=-0.11$,

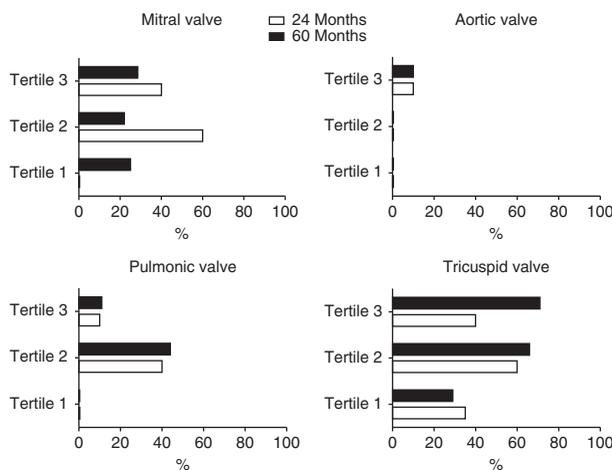


Figure 2 Prevalence of mitral (upper left panel), aortic (upper right panel), pulmonic (bottom left panel), and tricuspid (bottom right panel) valve regurgitations in each tertile of CAB dose after 24 (white bars) and 60 (black bars) months of treatment with CAB. Compared with short-term evaluation, prevalence of each valve insufficiency did not significantly change after long-term treatment with CAB. Particularly, a slight but not significant increase was found in the prevalence of mitral regurgitation (0 vs 25%, $P=0.27$) in tertile 1, pulmonic (40 vs 44%, $P=0.72$) and tricuspid (60 vs 66%, $P=0.84$) regurgitations in tertile 2, and tricuspid regurgitation (40 vs 71%, $P=0.47$) in tertile 3 (Fig. 2). Prevalence of tricuspid regurgitation in tertile 1 (35 vs 29%, $P=0.92$) and of mitral regurgitation in tertile 2 (60 vs 22%, $P=0.23$) and in tertile 3 (40 vs 28.6%, $P=0.9$) were even slightly reduced after 60-month CAB when compared with short-term evaluation.

$P=0.53$), pulmonic ($r=-0.01$, $P=0.93$), and tricuspid ($r=-0.10$, $P=0.55$) valve or grading of mitral ($r=-0.20$, $P=0.24$), aortic ($r=-0.11$, $P=0.53$), pulmonic ($r=-0.01$, $P=0.93$), and tricuspid ($r=-0.08$, $P=0.65$) valve regurgitations. At both evaluations, no correlation was found between dose tertiles and valve regurgitation ($r=-0.1$, $P=0.56$).

Discussion

This is the first prospective study to demonstrate that treatment with CAB does not increase the risk of clinically relevant valve regurgitation in patients with prolactinomas after the first 5 years of treatment. The DA-induced valve damage has been hypothesized to be mediated by the serotonergic system because these drugs have been demonstrated to have high affinity for the serotonin receptor subtype 2B, which is abundantly expressed in heart valves and is known to promote mitogenesis (43, 44). CAB and pergolide are reportedly potent agonists of these receptors, whereas other dopaminergic agents, including bromocriptine and lisuride, have antagonistic properties (44).

Results from 15 observational studies investigating the risk of fibrotic valvulopathy in hyperprolactinemic patients treated with CAB have been published to date (13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27). Two of them (15, 20) have shown no relevant findings. Four studies (16, 18, 21, 24) have demonstrated an increased prevalence of non-clinically relevant valve regurgitations, including mild tricuspid regurgitation (16, 21, 24), pulmonic insufficiency (16), or enlarged mitral tenting area (18). Ten trials (13, 14, 17, 18, 19, 22, 23, 25, 26, 27) have reported a variable prevalence, ranging from 2% (25) to 54% (13), of relevant valvulopathy including moderate-to-severe mitral or tricuspid insufficiency and mild aortic regurgitation, with the latter being observed only in two investigations (22, 24). Overall, a median CRVD rate of ~4% has been reported in hyperprolactinemic patients receiving treatment with CAB. In line with Delgado *et al.* (23), reporting no change in prevalence and grading of cardiac valve disease after 2-year treatment, the results of the current prospective study demonstrate no significant increase in the risk of CRVD after both 24 and 60 months of treatment with CAB. Moreover, even though trivial valvulopathy was slightly increased after long-term treatment, the overall prevalence of mitral (25%) and tricuspid (45%) valvular regurgitations has been found to be not increased when compared with the general population, in line with the results of the Framingham Heart Study (45), showing an overall prevalence of any degree of mitral and tricuspid regurgitations in 88–91 and 82–86% of the general population respectively. In our series, the prevalence of mild aortic insufficiency (2.5%) was similar to the 2.7% reported by Tan *et al.* (22), the 2%

recorded by Elenkova *et al.* (25), and the 3.9% found by Córdoba-Soriano *et al.* (26) and within the 0–14% described in the general population (45). In our cohort of patients, none developed significant pulmonic regurgitation or arterial pulmonic hypertension, and none showed moderate or severe regurgitation of mitral and tricuspid valve. These findings disagree with our previous data (13), showing a high prevalence (54%) of moderate tricuspid regurgitation in CAB-treated hyperprolactinemic patients. Particularly, we reported an approximately three times higher relative risk to develop moderate tricuspid valve regurgitation in treated patients compared with healthy controls and *de novo* patients (13). Interestingly, the increased prevalence of tricuspid insufficiency was found to be not associated with age, BMI, or blood pressure values but significantly CAB dose dependent (13), as already reported in patients with PD (14). In fact, moderate valve regurgitation was significantly more prevalent in patients who had been treated with a cumulative dose above the median (280 mg, 72%) than in those receiving lower doses (36%, $P=0.023$). It is noteworthy that patients with moderate tricuspid regurgitation had higher systolic and diastolic blood pressure when compared with those with no evidence of relevant valvulopathy (13). However, some important differences between the current results and our previous findings should be highlighted. In this study, median cumulative dose of CAB at both 2-year (48 mg) and 5-year evaluations (149 mg) was lower than that in our previous observation (280 mg) and much lower than that in patients with PD, usually treated with mean weekly doses up to 25 mg (7) and taking median cumulative doses ranging from 2600 to 6700 mg (8). Secondly, in our previous study (13), follow-up ranged from 16 to 250 months (median 74 months), whereas in the current prospective study, follow-up reached 60 months of observation. Albeit in patients with hyperprolactinemia, treatment duration has not been associated with the prevalence or severity of valvulopathy, and significant valvulopathy reportedly occurred more frequently in patients with PD after long-term treatment (5). Moreover, our previous data supported that tricuspid tethering area was significantly wider in treated patients than in controls and *de novo* patients (13). As previously shown in patients with PD (10, 46), CAB may induce subclinical fibrotic alterations in valve architecture predisposing to severe dysfunctions. The increased prevalence of subclinical regurgitations in hyperprolactinemic patients treated with CAB described in some reports (17, 18) would be consistent with this observation. Particularly, in the series by Kars *et al.* (17), mitral and aortic calcifications as well as leaflet thickening of the tricuspid valve were reported. Similarly, Lancellotti *et al.* (18) described mitral leaflet thickening in 6 of 102 patients receiving CAB and found that mitral tenting area, a quantitative index of valve restriction, was significantly higher in patients with mild

valvulopathy than in controls. We did not observe leaflet thickening in any patient, but after 24 months of therapy, the echocardiographic evaluation recorded aortic root dilatation and fibrosis only in a 61-year-old man (2%) affected with poorly controlled stage 2 arterial hypertension and with hypopituitarism on replacement therapy. Interestingly, this patient required high-dose treatment (5 mg) after 39 months of follow-up because of a partial resistance to medical therapy, but mild aortic fibrosis and dysfunction were diagnosed after 2-year therapy at a weekly dose of 1.5 mg.

In conclusion, the results of the current prospective study demonstrate that long-term CAB is not associated with an increased risk of CRVD in patients with prolactinomas. Nevertheless, besides the profibrotic effect largely and extensively described in patients with PD, several clinical conditions, including older age, systemic arterial hypertension, and gender, may increase the rate and severity of cardiac valve damage in patients with hyperprolactinemia. Therefore, in such patients, a careful echocardiographic investigation is mandatory. Further studies are needed to extend and confirm these data.

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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