

## Potential Cardiac Valve Effects of Dopamine Agonists in Hyperprolactinemia

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**Context:** An association has been demonstrated between valvular heart disease and dopamine agonist use in patients treated for Parkinson's disease. Following these reports, concern has been raised among endocrinologists about the safety of long-term treatment with dopamine agonists in hyperprolactinemic patients. The article will summarize all currently published research regarding the possible risk of valvulopathy in hyperprolactinemic patients on dopamine agonists and provide guidance based on current findings.

**Evidence Acquisition:** The major source of data acquisition included PubMed search strategies. PubMed was searched for publications containing the terms "valve," "valvular," or "valvulopathy," and one of the terms "dopamine agonists," "cabergoline," "bromocriptine," "pergolide," "prolactin," "prolactinoma," or "hyperprolactinemia." All publications from 1950 to August, 2008, were screened for use in this review.

**Evidence Synthesis:** The majority of studies showed no risk of valvular regurgitation associated with cabergoline. However, an increased risk of mild to moderate regurgitation, usually at the tricuspid valve, was reported in a few studies. Only one study suggested a relationship with the mean cumulative dose of cabergoline.

**Conclusions:** Although most reports do not show an association between use of dopamine agonists and valvulopathy, caution must be exercised, especially in patients requiring long-term, high-dose medication regimens. Clinicians should recommend the lowest possible doses of dopamine agonists and address the question of echocardiographic monitoring on an individual basis. (*J Clin Endocrinol Metab* 95: 1025–1033, 2010)

### Introduction

Dopamine agonists, specifically cabergoline and bromocriptine, represent first-line therapy for the treatment of prolactinomas. Cabergoline is commonly used in hyperprolactinemic patients due to its high clinical efficacy, tolerability, and favorable pharmacokinetic profile. Administered in doses as low as 0.5–1 mg weekly, cabergoline normalizes prolactin levels and restores gonadal function (1). It also promotes tumor shrinkage in patients with macroprolactinomas (2). Although cabergoline has been widely used for many years, concern has recently been raised about its long-term safety.

### Findings in Parkinson's Disease

Observational studies and case reports have shown an association between valvular heart disease and dopamine agonist therapy in patients with Parkinson's disease (3–6). As early as the 1990s, there were reports describing the occurrence of valvulopathy as well as constrictive pericarditis related to the use of cabergoline and, especially, pergolide in such patients (7, 8). Two recent large studies have further strengthened the association between valvular heart disease and high-dose dopamine agonist use in patients with Parkinson's disease (9, 10). One study reported that the incidence of moderate and severe valve regurgi-

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Abbreviation: BMI, Body mass index; CI, confidence interval; OR, odds ratio.

tation was 23.4 and 28.6% in patients treated with cabergoline or pergolide, respectively, significantly higher than in non-ergot-derived dopamine agonist-treated patients or controls (9). Of note, patients with clinically significant regurgitation had been exposed to a higher cumulative dose ( $4015 \pm 3208$  mg) of cabergoline than patients with less severe regurgitation ( $2341 \pm 2039$  mg) (9). The association between the cumulative dose of cabergoline and the risk and clinical relevance of valve regurgitation in Parkinson's disease was confirmed by other studies (11, 12). A population-based study of 11,417 subjects observed an increased risk of newly diagnosed valve regurgitation in patients treated with pergolide or cabergoline, particularly at daily doses higher than 3 mg/d and administered for 6 or more months. No increased risk was observed for bromocriptine, lisuride, pramipexole, or ropinirole (10). The withdrawal of pergolide from the U.S. market in 2007 was a direct consequence of these publications (13).

A recent review of all reports of fibrotic reactions associated with the use of dopamine agonists within the U.S. Adverse Event Reporting System database identified 159 cases of valvular regurgitation in patients on ergot-derived agents, and most of the patients (57%) were taking cabergoline (14). Although this report did not make any distinction between patients with Parkinson's disease and those with hyperprolactinemia, it showed that the risk for valvular regurgitation associated with ergot-derived medications was significantly dose-dependent [odds ratio (OR), 79; 95% confidence interval (CI), 52.7–114.5, for lower; *vs.* OR, 288; 95% CI, 210.5–390.6, for higher doses) (14).

## Potential Mechanisms of Fibrosis

The serotonergic system plays an important role in cardiac development and structure, and the serotonin 5HT<sub>2B</sub> receptor is particularly important. Inactivation of the 5HT<sub>2B</sub> gene receptor increases the lethality rate in mice embryos and newborns due to myocardial abnormalities, including defects in the subepicardial layer and lack of ventricular trabecular cells (15). Severe ventricular hypoplasia due to defective proliferation of myocytes was observed in surviving newborn mice, whereas myocyte derangement and a marked dilation of heart chambers were consistently found in adults (15). Valvular fibrosis was also observed in mice lacking the serotonin transporter, a molecule regulating serotonin clearance, suggesting that several receptor and postreceptor mechanisms may be implicated in the pathogenesis of dopamine agonist-related valvulopathy (16).

Typically, the morphological and histological features of dopamine agonist-related valvular disease resemble valves of subjects taking the serotonergic appetite suppressants fenfluramine and dexfenfluramine, as well as of patients affected by serotonin-secreting carcinoid tumors. It is a restrictive valvulopathy characterized by the spread of noncalcific fibrous plaques to the valve leaflets and the subvalvular apparatus, including the chordae tendinae, with consequent thickening and restriction of the valvular ostium (17).

In 2000, Rothman *et al.* (18) confirmed the role of the serotonergic system in the development of fenfluramine/dexfenfluramine-related valvular disease and identified the activation of the 5HT<sub>2B</sub> receptor as the pathogenic key event. Stimulation of the 5HT<sub>2B</sub> receptor causes excessive proliferation of fibromyoblasts, leading to a valvulopathy (17). Several molecules other than fenfluramine and its metabolites show high affinity to the 5HT<sub>2B</sub> receptor, including cabergoline and pergolide. Bromocriptine and quinagolide have weaker affinity for the 5HT<sub>2B</sub> receptor and, therefore, are thought to be less valvulopathic. However, in 2002, a case report was published describing the occurrence of triple valvular fibroplasia and severe tricuspid regurgitation in a 63-yr-old man with Parkinson's disease who had been treated with 40 mg/d of bromocriptine for 30 months (19). From the U.S. Adverse Event Reporting System database, three cases of valvular regurgitation and 10 cases of pleural fibrosis or pulmonary changes associated with the use of bromocriptine were reported (14). Several case reports outside the United States had previously documented the occurrence of pleuropulmonary fibrosis in Parkinson's patients taking high doses of bromocriptine (20–22).

After the studies on Parkinson's patients, concern has been raised among endocrinologists about the safety of long-term treatment with dopamine agonists, especially those with higher affinity to the 5HT<sub>2B</sub> receptor.

## Cardiac Valve Abnormalities in the Normal Population

Before considering the possible role of dopamine agonists in cardiac valve disease in hyperprolactinemia, it is important to address the prevalence and significance of valve abnormalities in the normal healthy population. Studies on the prevalence of valvular regurgitation in normal subjects have shown extremely variable results, depending on the design of each study, the echocardiographic technique used, as well as size and characteristics of the samples analyzed (23). For example, in published reports, the prevalence rate of tricuspid regurgitation ranged from 24 to 96%, whereas that of mitral regurgitation was from 10 to

80%, and both of them significantly increased with advancing age (23, 24). Moreover, age was related positively to the severity of the regurgitation (23).

In a population-based cohort, the Framingham Heart Study (23), a color Doppler echocardiographic examination was performed in 1696 men and 1893 women (aged  $54 \pm 10$  yr) to evaluate the prevalence of regurgitation at mitral, tricuspid, and aortic valves. Many subjects in the study had several clinical variables potentially associated with valvulopathy, including hypertension, diabetes, hypercholesterolemia, smoking, and history of myocardial infarction or congestive heart failure.

Mitral regurgitation of any degree, including trace regurgitation, was the most common, detected in 87.7% of men and 91.5% of women; any degree of tricuspid regurgitation was also frequent, found in 82% of men and 85.7% of women. However, an important point is that the vast majority of these findings were not clinically significant. Regurgitation classified as mild or more than mild, which is considered clinically significant at these valves according to the criteria used by the authors, occurred in about 19% in both sexes for the mitral valve, whereas it was 14.8% in men and 18.4% in women for the tricuspid valve. Any degree of aortic regurgitation was observed in 13% of men and 8.5% of women. Aortic regurgitation more than or equal to mild was observed in 0 to 14% over a wide age range in both sexes (23).

These study subjects, which represent a population-based cohort, include patients with hypertension and other cardiac risk factors. Thus, they would not necessarily be classified as “normal,” but these data clearly demonstrate a high rate of valve abnormalities in the adult population unrelated to dopamine agonist use.

## Cardiac Valve Abnormalities in Patients with Hyperprolactinemia

### Summary of published findings

A number of reports investigating potential cardiac valve abnormalities in cabergoline-treated patients with prolactinomas have been published and have been summarized in Table 1. Overall, these reports appear reassuring, although there are no long-term controlled studies published to date.

In all these studies, valvular regurgitations were defined and graded according to the recommendations of the American Society of Echocardiography, as absent (grade 0), trace (grade 1), mild (grade 2), moderate (grade 3), or severe (grade 4). Valvular regurgitation considered to be clinically significant was at least moderate mitral or tricuspid regurgitation, at least mild aortic regurgitation, and greater than mild pulmonic regurgitation (25).

Colao *et al.* (26) studied 50 patients receiving cabergoline and found a significantly higher prevalence (54%) of moderate tricuspid regurgitation as compared with 50 age- and sex-matched controls (0%) recruited from the medical staff, and a control group of 20 subjects with *de novo* hyperprolactinemia (18%). The occurrence of moderate tricuspid regurgitation was significantly more frequent among the patients who had been treated with a cumulative dose of cabergoline above the median (72%) than those receiving lower doses (36%) (26). In this study, it was not specified how many echocardiographers read the scans.

Of note, patients with moderate tricuspid regurgitation also had a higher systolic and diastolic blood pressure as compared with those not having clinically relevant valve abnormalities. It is therefore possible that blood pressure was a contributing factor. The Framingham Heart Study showed that systemic hypertension was a significant determinant of mitral, but not tricuspid, regurgitation (23), and this was confirmed in a cohort of 223 Japanese patients with Parkinson's disease (27). In the latter study, elderly, hypertensive patients receiving cabergoline or pergolide were at higher risk of left-sided valvulopathy than younger patients with normal blood pressure (27). However, in the study by Colao *et al.* (26) patients on cabergoline had significantly higher mean systolic and diastolic blood pressure than controls, a finding that has not been described in other reports evaluating a possible valvulopathic effect of cabergoline in hyperprolactinemic patients (28, 31, 34).

The observation of a clinically significant degree of valve regurgitation (moderate) by Colao *et al.* (26) has not been confirmed by many other reports (26, 28–35). In particular, Bogazzi *et al.* (28) evaluated 100 subjects and showed that in cabergoline-treated patients, the prevalence of clinically relevant regurgitation at any valve was not different in comparison to age- and sex-matched controls recruited from healthy medical staff members. In this study, a single operator was involved in the review of the scans (28). Vallette *et al.* (29) evaluated 70 subjects with prolactinomas who had been taking cabergoline for a mean duration of 55 months and detected moderate valvular regurgitation in 5.7% of patients, a finding not significantly different from the prevalence of 7.1% in age- and sex-matched controls. It should be highlighted that Vallette *et al.* (29) in the same group pooled patients with no regurgitation together with those with mild valvulopathy, making it difficult to compare these findings with other reports that strictly followed the definitions in the American Echocardiographic Society guidelines (25). Herring *et al.* (30) studied 50 patients with prolactinomas

**TABLE 1.** Studies of cardiac valves and cabergoline use in patients with hyperprolactinemia

First author, year (Ref.)	No. of patients	Gender (M/F)	Age (yr) (mean ± sd)	Cumulative cbg dose (mg), mean ± sd (range)	Treatment duration (months), mean ± sd (range)	Valvulopathy moderate/severe	Association with cumulative dose	Comments	Echocardiographer Characteristics	
									n	Blinded
Bogazzi, 2008 (28)	100	21/79	41 ± 13	279 ± 301 (15–1327)	67 ± 39 (3–199)	7% (moderate)	No	Regurgitation grade at each valve and mean total regurgitation score not different from controls	1	n/a
Colaço, 2008 (26)	50	6/44	36 ± 10	414 ± 390 (32–1938)	74 (median) (16–260)	54% (moderate)	Yes	Higher prevalence of moderate tricuspid regurgitation in patients than in controls	n/a	n/a
Devlin, 2008 (35)	45	14/31	41 ± 10	146 ± 220	39 ± 29	0%	No	Prevalence of valve abnormalities not different from that reported in normal populations	Several	No
Wakil, 2008 (33)	44	12/32	42 ± 13	311	44.8	0%	No	Higher prevalence of mild tricuspid and pulmonary regurgitation in patients than in controls	1	No
Kars, 2008 (32)	78						No	Mild tricuspid regurgitation more prevalent in group A than either group B or controls. Aortic calcifications more prevalent in groups A+B and A alone than controls; mitral calcifications and thickening of the tricuspid leaflets more prevalent in group A than controls	1	Yes
Lancellotti, 2008 (34)	102	29/73	51 ± 14	204 (median) (18–1718)	79 (median) (12–228)	1.9%	No	Regurgitation grade at each valve not different from controls; significantly higher mitral tenting area in patients	2	PB
Nachtigall, 2009 (31)	100	48/52	44 ± 13	253 ± 52 (15–2520)	48 ± 4 (6–200)	0%	No	Regurgitation grade at any valve not different from controls	Several	Yes
Vallette, 2009 (29)	70	33/37	44	282 ± 271	55 ± 22	5.7%	No	Regurgitation grade at any valve not different from controls	2	PB
Herring, 2009 (30)	50	30/20	51 ± 2	443 ± 53	79 ± 6 (12–156)	0%	No	Regurgitation grade at any valve, valvular thickening and mitral valve tenting area not different from controls	2	PB

M, Males; F, females; cbg, cabergoline; DA, dopamine agonists; CD, cumulative dose; n/a, not available; PB, partially blinded. All echocardiograms were performed by two experienced operators and interpreted by a third echocardiographer who was blinded to the study group (29, 30, 34).

taking cabergoline at a higher cumulative dose than in other studies and did not find any difference in the prevalence of regurgitation at any valve as compared with age- and sex- matched controls with normal left ventricular function (Table 1).

In a series described by Nachtigall *et al.* (31), mild aortic regurgitation was reported in only 1 of 100 patients treated with a mean cumulative dose of  $253 \pm 52$  mg, which was not different from that described in this age range in the Framingham Study (23). Overall, Nachtigall *et al.* (31) found no difference in the prevalence of valve regurgitation at any valve of either minor or severe degree in 100 patients compared with an equal number of controls who were carefully matched one-to-one for age, sex, body mass index (BMI), and blood pressure. Moreover, Nachtigall *et al.* (31) also found that the prevalence of any degree of regurgitation (including trace) affecting more than one valve was 75% in patients, which was not significantly different compared with controls. The inclusion of a matched control group appears particularly important in light of the previous observations showing factors that are significant determinants of valvular regurgitation in the general population (23, 24). Importantly, the operators reading the echocardiograms in this study were blinded (31).

Another report studying 78 patients (47 treated with cabergoline and 31 treated with other medications, including bromocriptine, or surgery) did not find any difference in the prevalence of moderate/severe valvular heart disease in patients on dopamine agonists compared with 78 healthy controls recruited from a database and matched for age, gender, BMI, and ventricular systolic function. However, the frequency of mild tricuspid regurgitation was higher in patients who had been administered cabergoline than in healthy subjects (43 vs. 26%;  $P = 0.050$ ) (32). Similarly, Wakil *et al.* (33) observed an increased prevalence of mild tricuspid and pulmonary regurgitation in a series of 44 patients treated with cabergoline compared with 566 healthy controls who had undergone echocardiography for palpitations [OR, 3.1; 95% CI, 1.0–9.6;  $P = 0.04$  for tricuspid; and OR, 7.8; 95% CI, 0.8–78.4;  $P < 0.001$  for pulmonary). No moderate or severe regurgitation was observed in this series (33). Yet, it should be highlighted that prevalence of mild tricuspid regurgitation in the study by Kars *et al.* (32) at 43% is not significantly different from the prevalence to up to 40% in the general population as reported in some series (24, 25). Thus, larger prospective controlled studies are required to confirm a real causative effect of cabergoline use on this otherwise common finding.

### Effect on other echocardiographic parameters

Of note, Kars *et al.* (32) described some additional effects in the cabergoline group, including a significant appearance of mitral and aortic calcifications as well as leaflet thickening of the tricuspid valve. Colao *et al.* (26) showed that tricuspid tethering area was significantly wider in patients than in controls ( $P < 0.0001$ ).

Other studies could not confirm these findings and did not report any significant difference in leaflet thickening at any valve between patients on cabergoline and controls (29, 30, 33). Although Lancellotti *et al.* (34) found that six of 102 patients receiving cabergoline had mitral valve leaflet thickening, their cumulative dose was slightly lower than that observed in subjects without any sign of valvular restriction.

In the prospective study by Lancellotti *et al.* (34) including 102 subjects receiving cabergoline, an equal distribution of valvular disease was noted in those patients and 51 age- and sex-matched controls recruited from medical staff or from subjects who underwent echocardiography for evaluation of fitness or coronary risk. Nonetheless, the same authors also found that mitral tenting area, a quantitative index of valvular restriction, was significantly higher in patients on cabergoline. Mitral tenting area, which proportionally increased with the severity of the regurgitation, was significantly greater in patients on cabergoline with mild valvulopathy as compared with controls (34). Conversely, Herring *et al.* (30) did not find any difference in the mitral valve tenting area and height between patients on cabergoline vs. controls. In Parkinson's patients on treatment with pergolide or cabergoline, a significantly greater mitral tenting area was documented compared with controls, even in those with no regurgitation (9). The clinical meaning of these findings remains to be elucidated because in Parkinson's patients, mitral tenting area was found to be large regardless of treatment (5), but cabergoline may induce early, subclinical alterations of the valve architecture, predisposing to more severe and clinically evident changes as the treatment continues. The higher prevalence of subclinical regurgitation in patients on cabergoline described in some reports (32, 33) would be consistent with this observation.

### Is the valvulopathic effect of dopamine agonists dose-dependent?

There is substantial overlap between the mean cumulative dose of cabergoline used for hyperprolactinemic patients in each report. No association has emerged between the cumulative dose and pathological valvular characteristics in most reports, contrary to what has been observed in Parkinson's patients. This discrepancy may be partly accounted for by the fact that the cumulative dose of

cabergoline commonly employed in hyperprolactinemic patients is significantly lower than that used in Parkinson's. It is also possible that differences in the velocity at which the peak dose is reached or duration of exposure may also play a role (28–35). Nachtigall *et al.* reported that among patients taking a cumulative dose below or equal to the median ( $\leq 116$  mg), 17% had greater than trace regurgitation of any valve, compared with 13% of those on a cumulative dose above the median ( $P = 0.55$ ) (31). In the study by Bogazzi (28), although subjects with moderate valvulopathy had been given lower cumulative doses of cabergoline and for shorter periods of time than those with the lowest grading of regurgitation, the difference was not significant. Although patients described by Herring *et al.* (30) were taking a higher mean cumulative dose ( $443 \pm 53$  mg) as compared with that in other studies, they did not find any correlation between the prevalence of significant regurgitation and the cumulative dose of cabergoline.

However, patients described by Colao *et al.* (26) took a mean cumulative dose equal to  $413.9 \pm 390.4$  mg (range, 32–1938) which was slightly higher than reported in most of the other studies and, as mentioned above, the majority of subjects with moderate regurgitation had a cumulative dose above the median (Table 1). Kars *et al.* (32) did not find any association between the occurrence of clinically significant regurgitation and the cumulative dose of cabergoline. They observed that eight of nine patients with more severe valvular regurgitation were treated with a mean cumulative dose of 388 mg for more than 72 months, which was not statistically above the mean values for the total group (32).

Ono *et al.* (36) evaluated the normalization rate of hyperprolactinemia in patients having prolactinomas resistant to the therapy, who needed high doses of cabergoline (up to  $5.2 \pm 0.6$  mg/wk). Although they did not show the echocardiographic data in detail, they state that none of the 106 patients who were taking cabergoline at doses greater than or equal to 1 mg/wk were diagnosed with clinically relevant valvulopathy (36).

Overall, these inconsistent findings do not completely exclude a relationship between high doses of cabergoline and the incidence of valvulopathy, especially in some hyperprolactinemic patients who may potentially retain an individual susceptibility to the deleterious effects of this medication on valvular apparatus (5). An individual vulnerability has been advocated to explain why fibrous valvulopathy occurs in less than half of patients taking ergot-derived medications (5). Polymorphism of the 5HT<sub>2B</sub> receptor may be the basis of this variable effect (37). Preliminary pharmacogenetic studies have characterized genetically based differences in the therapeutic re-

sponse to several psychotropic drugs (38). In particular, polymorphisms of serotonin-related genes such as 5HT<sub>1A</sub> and 5HT<sub>2C</sub> have been associated with interindividual variations in the response to clozapine, and it has been hypothesized that they may also influence some drug-related changes in eating behavior (38). It has been shown that some allelic variants of the 5HT<sub>2B</sub> gene tend to be associated with drug abuse vulnerability and alcoholism (39).

### Differences between Parkinson's and hyperprolactinemic patients

It should be highlighted that some important differences exist between the dose and duration of cabergoline treatment for Parkinson's disease and the use of this medication in hyperprolactinemia. Mean weekly doses of dopamine agonists are typically much higher in patients with Parkinson's disease who may take up to 25 mg/wk in contrast to the 0.5–3.0 mg/wk typical in hyperprolactinemia. However, the mean duration of treatment is significantly lower in Parkinson's disease at  $24.4 \pm 15.4$  months (9) than in individuals treated for hyperprolactinemia who may remain on cabergoline for many decades. In fact, as shown in Table 1, duration of treatment in the studies on hyperprolactinemic patients published so far ranged between a minimum of 12 up to 260 months, with a median duration of 74 and 79 months in the studies by Colao *et al.* (26) and Lancellotti *et al.* (34), respectively (26, 28–35). The cumulative dose of cabergoline in several studies on Parkinson's disease ranged between 2600 and 6700 mg (37), whereas it ranged between 200 and 443 mg in the reports on hyperprolactinemic patients published so far. Yet, it should be underscored that because of the longer duration of treatment, individual cumulative dose in some hyperprolactinemic patients taking cabergoline was closer to that taken by Parkinson's patients. For instance, the maximum cumulative doses reported in the studies by Nachtigall *et al.* (31) and Colao *et al.* (26) were 2520 and 1938 mg, respectively.

Additionally, patients treated for hyperprolactinemia usually begin treatment at a much younger age than Parkinson's patients. It should be emphasized that advancing age is strongly associated with increasing prevalence of valvulopathy in either one or multiple valves in the general population, and it has been found to be significantly and positively related to the severity of regurgitation in both sexes (23, 24).

In future studies, particular attention should be paid to patients who have been exposed to high cabergoline doses for a prolonged period of time. As mentioned above, in the paper by Kars (32), eight of nine patients with clinically significant valve regurgitation had received cabergoline

for a mean period of 6.4 yr. However, Bogazzi *et al.* (28) did not find any significant difference in the valve score of the four patients receiving a dose higher than 3 mg/wk for more than 6 yr, although the low number of subjects analyzed makes it difficult to draw inferences from this finding.

Gender is another important difference between patients who have hyperprolactinemia and those with Parkinson's disease, in that male predominance is observed in the latter group. This observation is particularly interesting because gender appears to be one of the variables independently associated with valve regurgitation in large population-based studies (23, 40). In the Framingham Heart Study, it was found that women were significantly more likely to have more than or the same degree of mild tricuspid regurgitation as compared with men. At multivariate regression analysis, female and male gender were significant determinants of tricuspid and aortic regurgitation, respectively (23). Nachtigall *et al.* (31) did not find any intergender difference in the prevalence of regurgitation at any valve when the entire cohort of 58 female and 48 male patients with hyperprolactinemia was considered. However, when genders were analyzed separately, female patients had more mild tricuspid regurgitation than matched female controls (15.4 vs. 1.9%;  $P = 0.03$ ) (31). These data are in accordance with those reported by Wakil *et al.* (33) and Kars *et al.* (32) who found higher prevalence of mild tricuspid regurgitation in their cohorts, which included more than twice as many women as men.

### Safety of bromocriptine

No study has extensively evaluated the potential valvulopathic effects of bromocriptine in hyperprolactinemic patients, but some reports regarding patients on cabergoline showed that previous treatment with bromocriptine was not associated with a different prevalence of regurgitation compared with either patients who had been steadily on cabergoline or normal controls (28, 29, 32, 34). In particular, Kars *et al.* (34) found that valvular heart disease reached the borderline of significantly increased prevalence in patients treated exclusively with cabergoline compared with a small group of control subjects who had different therapies, including bromocriptine (32). The low number of patients included in these subgroups represents an important limitation that should be taken into consideration.

### Limitations of published studies

Future studies that can conclusively ascertain the safety or risk of cabergoline in hyperprolactinemic patients should be longer, longitudinal, and ideally double-blind, although the latter is likely not feasible. The issue of the

reproducibility and standardization of echocardiographic measurements must also be addressed. In addition to the well-known interoperator and interinstrument variability, several technical and hemodynamic factors influence echocardiographic accuracy in the assessment of valvular regurgitation, especially those at the lowest degrees (25). Moreover, a rigorous choice of control subjects should be performed to avoid selection bias. For instance, in some reports, controls were selected among subjects with clinical indications for echocardiography (32, 33) or healthy patients without clinically significant findings (31). In the study by Devin *et al.* (35), there was no control group, and prevalence of valve regurgitation was compared with that previously reported in normal populations. Even when control groups were randomly recruited from apparently normal people (*e.g.* medical staff) (26, 28), they might not be fully representative of the general population, due to the small sample size and homogeneous pool of subjects. Controls should be carefully matched for any potential determinant of valvular function, including age, gender, BMI, and blood pressure (23, 24).

A recent meta-analysis published by Bogazzi *et al.* (41), which pooled together the results of six clinical studies on the effects of cabergoline in hyperprolactinemic patients (26, 28, 30, 32–34), showed a significant increase in risk of mild plus moderate tricuspid valve regurgitation in the total group of 393 subjects (prevalence ratio, 1.40; 95% CI, 1.17–1.67). However, the authors emphasized that only one among the studies analyzed (26) found a higher prevalence of moderate regurgitation and concluded that the clinical relevance of their finding is still difficult to establish.

### Clinical Practice Suggestions

Although data reported so far substantiate the need for further investigation, they also offer practical information for endocrinologists (42). The ergot-derived dopamine agonists increase the risk of valvular heart disease in Parkinson's patients and in a few, but not most, reports of hyperprolactinemic patients. The affinity of each agonist for the 5HT<sub>2B</sub> receptor, other cardiac risk factors including hypertension, or genetic susceptibility may determine the risk of valve disease for specific agents. Insufficient evidence is available to make a consensus statement about the optimum treatment for each patient. Although bromocriptine may have a lower risk of valvulopathy, it is associated with lower tolerability and therapeutic efficacy in terms of prolactin normalization and tumor shrinkage as compared with cabergoline; and due to its short half-life, it requires more frequent dosing (43).

Patients taking these dopamine agonists, particularly cabergoline, should be educated about the potential risks associated with their use, and the role of echocardiographic monitoring should be decided on an individual basis. Moreover, treatment with these drugs should be recommended at the lowest dose and for the shortest duration possible. In some carefully selected individuals with prolactinomas, withdrawal of dopamine agonist therapy appears to be possible, without negative clinical consequences (1, 44, 45). Non-ergot-derived dopamine agonists such as quinagolide (not currently available in the United States), pramipexole, and ropinirole may represent other therapeutic options.

Large, prospective, controlled studies are needed to permit evidence-based recommendations to be made about whether echocardiograms should be performed. Until then, it is important that patients be informed of the available data and be aware of the option of echocardiography. At our center, we discuss the theoretical risks of dopamine agonist therapy with each patient receiving cabergoline. We explain the potential risks based on the current knowledge and offer an echocardiogram. Baseline echocardiograms are usually obtained on patients who are likely to be treated long-term with cabergoline. Based on the largely reassuring information published to date, the need for follow-up scans is evaluated individually depending on clinical symptoms, dose, and duration rather than being performed routinely in every patient. We advise prolactinoma patients on high doses of cabergoline to undergo an echocardiogram regularly (every 1–2 yr) because it is unknown whether these patients are at an increased risk of long-term valvular abnormalities.

## Conclusions

We have reported and analyzed the results from all nine studies published to date investigating a possible relationship between the use of cabergoline and valvular heart disease in patients with hyperprolactinemia. Overall, 639 subjects were evaluated in these papers.

Although most of them do not show an increased occurrence of clinically relevant valvulopathy, caution must be exercised, especially in patients requiring long-term, high-dose medication regimens. Large, multicenter, long-term, prospective studies are necessary to answer several unresolved questions and conclusively assess the safety of dopamine agonists, at various doses and durations, in patients with hyperprolactinemia. Until then, it is advisable to share the most current knowledge with patients in deciding on individual treatment and monitoring options.

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