

# Cabergoline and valvulopathy in patients treated for hyperprolactinemia

- an overview of the current literature

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## Studies on valvular heart disease in patients with hyperprolactinemia treated with cabergoline

Author (year)	Number of patients F=female Mean age ( $\pm$ SD)	Number of controls (* data from an echocardiographic database)	Cumulative dose of cabergoline mean ( $\pm$ SD) mg (range)	Treatment duration mean ( $\pm$ SD) (range) months	Significant valve regurgitation (=SVR) Patients vs. controls	Mitral valve tenting area
Bogazzi (2008)	<b>100</b> 79% F 41 ( $\pm$ 13) yrs	100	<b>279</b> ( $\pm$ 301) (15-1327)	<b>67</b> ( $\pm$ 39) (3-199)	No difference in SVR	-
Kars (2008)	<b>47</b> 74% F 47 ( $\pm$ 1.4) yrs	78*	<b>363</b> ( $\pm$ 55) (24-1768)	<b>62</b> ( $\pm$ 4.8) (12-124)	No difference in SVR Increased mild TR and aortic valve calcification	-
Valette (2008)	<b>70</b> 53% F 44 ( $\pm$ 13) yrs	70	<b>282</b> ( $\pm$ 271) Median 180 (25-1248)	<b>55</b> ( $\pm$ 22) (12-90)	No difference in SVR	-
Lancelotti (2008)	<b>102</b> 72% F 51 ( $\pm$ 14) yrs	51	Median <b>204</b> (18-1718)	<u>Median 79</u> (12-228)	No difference in SVR	Significantly higher in patients
Wakil (2008)	<b>44</b> 73% F 42 ( $\pm$ 13) yrs	566*	<b>311</b> Median 86	<b>45</b> mån Median 33 mån	No difference in SVR Increased mild TR and mild PR	-
Colao (2008)	<b>50</b> 88% F 36.5 ( $\pm$ 10.5) yrs	50	<b>414</b> ( $\pm$ 390) Median 280 (32-1938)	<b>81</b> ( $\pm$ 37) Median 74 (16-250)	Increased moderate TR More frequent with cumul. dose >280 mg	Tricuspid valve tethering area sign. wider in patients
Herring (2009)	<b>50</b> 40% F 51( $\pm$ 2.2) yrs	50	<b>443</b> ( $\pm$ 53) (52-1872)	<b>79</b> ( $\pm$ 6) (12-156)	No SVR	Not significantly greater in patients
Nachtigall (2009)	<b>100</b> 52% F 44 ( $\pm$ 13) yrs	100*	<b>253</b> $\pm$ 52 (SEM) (15-2520)	<b>48</b> $\pm$ 4 (SEM) (6-200)	No difference in SVR Women increased mild TR	-

**Treatment with low doses of cabergoline is not associated with increased prevalence of cardiac valve regurgitation in patients with hyperprolactinaemia.**

Bogazzi F *et al.* Int J Clin Pract, 2008;62:1864-9.

- 100 patients with hyperprolactinemia
  - 79 women, 31 men. Mean age 41 ( $\pm$ 13) years
  - 60 microprolactinomas, 39 macroprolactinomas, 1 patient with non tumoural hyperprolactinemia
  
- 100 controls, recruited among the medical staff at the hospital - matched for sex, age and BMI
  
- No difference in prevalence of arterial hypertension, diabetes, hypercholesterolemia or smoking habits between patients and controls. No patient or control had a positive history of cardiovascular or cardiac valve disease.
  
- Mean cumulative dose: 279  $\pm$  301 mg (range: 15-1327 mg)
- Mean weekly dose: 1.1  $\pm$  0.9 mg (range: 0.25-3.5 mg)
- Treatment duration: mean 67  $\pm$  39 months (range: 3-199 months)

- **No difference in prevalence of moderate regurgitation** between patients and controls (patients (7%) vs. controls (6%), (p=0.980))
- Moderate valve regurgitation was not associated with the duration of treatment (p=0.359), the cumulative dose of cabergoline (p=0.173) or with age (p=0.281)
- Echocardiographic grading at each valve did not differ between patients and controls
- 4 patients; received a weekly dose of cabergoline > 3 mg, > 6 years  
⇒ Cardiac valve score was not different from that of the remaining subjects

## **Aortic valve calcification and mild tricuspid regurgitation, but no clinical heart disease after 8 years of dopamine agonist therapy for prolactinoma.**

Kars M *et al.* JCEM, 2008;93:3348-56

- 78 patients with prolactinomas  
74% women, mean age  $47 \pm 1.4$  yr, 69% microprolactinomas
  - Group 1: Patients treated with cabergoline (n=47)  
Treatment duration  $5.2 \pm 0.4$  yr (1-10.3 yr)  
Cumulative dose  $363 \pm 55$  mg (24-1768 mg)
  - Group 2: Patients treated with bromocriptine, terguride, quinagolide or patients who received other treatment modalities such as surgery, (n=31)
- 78 controls from an echocardiography database – matched for age, gender, body surface and left ventricular systolic function
- Mean duration of dopamine agonist treatment was  $8 \pm 0.6$  yr (range: 0-24 yr)

- **No difference in prevalence of clinically significant valve regurgitation between patients and controls**  
Patients vs. controls, 12% vs. 17%, (p=0.141)  
Group 1 vs. group 2; 17% vs. 3%, (p=0.062)
- **Mild tricuspid valve regurgitation** present in 41% of patients vs. 26% of controls, (p=0.042)  
Group 1 vs. group 2; 43% vs. 39%, (p=0.736)
- **Aortic valve calcification** present in 40% of patients vs. 18% of controls (p=0.003)  
Group 1 vs. group 2; 45% vs. 32%, (p=0.273)
- No relation between cumulative dose of cabergoline and the presence of valve regurgitation (mild, moderate or severe)

## **Long-term cabergoline therapy is not associated with valvular heart disease in patients with prolactinomas.**

Vallette S *et al*, Pituitary, July 2008

- 70 patients with prolactinomas
  - 53% women, mean age 44±13 years, 33% microadenomas
  - Treated with cabergoline for at least 1 year
  
- 70 controls – matched for sex and birth year

The controls were identified from 120 consecutive subjects referred to a echocardiography laboratory. Subjects with known valvular, ischemic, or congenital heart disease were excluded. Of these, 70 were selected on the basis of age and sex matching.
  
- Mean cumulative dose: 282 (± 271) mg, (range 25-1248 mg)
  
- Mean treatment duration: 55 (± 22) months, (range 12-90 months)

- **No difference in the prevalence of moderate heart-valve disease** between patients and controls 5.7% vs. 7.1% (p=0.73)
  
- No correlation between the presence of significant heart-valve regurgitation and:
  - cabergoline cumulative dose
  - duration of cabergoline treatment
  - prior use of bromocriptine
  - age
  - pituitary adenoma size
  - prolactin levels

## Cabergoline and the risk of valvular lesions in endocrine disease

Lancelotti P *et al*, Eur J Endocrinol, 2008;159:1-5

- 102 patients treated with cabergoline for at least 1 year
  - 72% women, mean age 51±14 years
  - Received cabergoline for the treatment of prolactinoma (n=90), idiopathic hyperprolactinemia (n=6), and non-secreting pituitary adenoma (n=6).
  - Cumulative dose: median 204 mg (range 18-1718)
  - Treatment duration: median 79 months (range 12-228)
  
- 51 controls – matched for sex and birth year
  - The controls were recruited among healthy members of the hospital staff and from subjects attending the echocardiographic laboratory for evaluation of fitness or coronary risk factors
  
- The two groups were also matched for the presence of diabetes mellitus, hypertension, dyslipidemia and a history of coronary artery bypass grafting

- **No significantly increased risk of clinically relevant valvular regurgitation** between patients and controls (3% vs. 0%)

**Mitral valve tenting area was significantly greater** in patients than in controls, (p=0.03)

No correlation between mean tenting area and duration of cabergoline treatment or the cumulative dose

## **Low dose cabergoline for hyperprolactinaemia is not associated with clinically significant valvular heart disease**

Wakil et al, Eur J Endocrinol, 2008;159:R11-R14

- 44 patients with hyperprolactinemia
  - Mean cumulative dose: 311 mg (median 86 mg)
  - Weekly dose: range 0.25-4 mg
  - Mean treatment duration: 45 months (median 33 months)
  
- 566 controls
  - Controls was selected from an echocardiographic database. These controls were presenting with a complaint of palpitations with no other known underlying cardiac diagnosis or past medical history

- **No significant severe or moderate valvular regurgitation** in either patients or controls
  
- **Increased risk of mild tricuspid and pulmonary regurgitation** in the cabergoline group
  - Mild tricuspid regurgitation in patients vs. controls; 11% vs. 6.7%, (p=0.04) OR 3.1 (95% CI 1.0-9.6)
  - Mild pulmonary regurgitation in patients vs. controls; 2.3% vs. 0.5% (p<0.0001) OR 7.8 (95% CI 0.8-78.4)



## Increased prevalence of tricuspid regurgitation in patients with prolactinomas chronically treated with cabergoline

Colao A *et al.* JCEM, 2008;93:3777-84

- Study population
  - 50 patients with prolactinomas (88% women, mean age 36 years, 66% microprolactinomas)
  - 20 patients with newly diagnosed prolactinomas (85% women, mean age 28 år, 60% microprolactinomas)
  - 50 controls matched for sex and age (controls were recruited among relatives of the patients or acquaintances of the medical staff)
  
- Mean cumulative dose of cabergoline: 414 ±390 mg (median 280 (32-1938) mg)
  
- Treatment duration: mean 81 months, median 74 (range 13-128) months
  
- BMI, blood pressure values and left ventricular mass was significantly higher in treated patients than in *de novo* patients and controls

- No difference in the prevalence of mild regurgitation between treated patients vs. *de novo patients* vs. controls (for TR 30% vs. 55% vs. 42%)
- **Increased prevalence of moderate tricuspid valve regurgitation** – in treated patients compared to *de novo* patients, and controls; 54% vs. 0% vs 18%, ( $p < 0.0001$ )  
RR=3.0 (95% CI 1.6-5.8) patients vs. controls
- Moderate tricuspid valve regurgitation more frequent in patients receiving a cumulative dose above the median dose (280 mg)  
RR=2.0 (95% CI 1.2-3.7)
- Tricuspid tethering area significantly wider in patients compared to controls

## **Valvular heart disease and the use of cabergoline for the treatment of prolactinoma**

Herring N *et al*, Clin Endocrinol (Oxf) 2009;70:104-8

- 50 patients with prolactinomas
  - 48% macroprolactinomas, 52% microprolactinomas, 60% men, mean age 51 ( $\pm$  2.2) years
  - Mean cumulative dose: 443 ( $\pm$  53) mg, (range 52-1872 mg)
  - Mean treatment duration: 6.6 ( $\pm$  0.5) years, (range 1-13 years)
  
- 50 sex- and age-matched controls
  - Controls were recruited from patients referred for palpitations but found to have sinus rhythm with normal left ventricular dimensions and systolic function

- **No significant valvular thickening or regurgitation** of any valve in the prolactinoma group
- The prevalence of **mild valvular regurgitation not higher** in patients than in the case-control group
- **The mitral valve tenting area and height not greater** than in the control group. There was no correlation between tenting area or height and cumulative cabergoline dose.



## **Gender effects on cardiac valvular function in hyperprolactinemic patients receiving cabergoline: a retrospective study**

Nachtigall *et al*, Clin Endocrinol (Oxf) 2009 Apr 17. [Epub ahead of print]

- 100 patients with hyperprolactinemia (HPL) received cabergoline for at least 6 months
  - 52% women, mean age 44 ( $\pm$  13) years
  - 93 patients prolactinoma, 4 patients acromegaly and HPL, 3 patients HPL due to other sellar lesions
  - Mean cumulative dose: 253  $\pm$  52 (SEM) mg, (range 15-2520 mg)
  - Mean dose: 0.8  $\pm$  0.2 (SEM) mg/week, (range 0.3-17 mg/week)
  - Mean treatment duration: 48  $\pm$  4 (SEM) months, (range 6-200 months)
  
- 100 controls – matched for age, gender, BMI and hypertension
  - Controls were selected from a database of echocardiograms considered normal

- **No significant differences in valvular function** in patients compared to controls
- The prevalence of clinically significant valvular abnormalities was not greater than expected in a normal population (mild AR in 2 patients (2%))
- **No association** of valvular regurgitation and **cumulative dose**, mean dose or duration of treatment of cabergoline
- None of the four patients with acromegaly had significant valvular regurgitation
- Hyperprolactinemic **women** had **higher prevalence of mild TR** compared to controls (15.4% vs 1.9%,  $p=0.03$ )

## Cabergoline and valvulopathy in patients treated for hyperprolactinemia: Summary of 8 studies

- **No association** between treatment with cabergoline and **clinically significant valve regurgitation** in **7 studies**
- In **one study** increased prevalence of **moderate tricuspid valve regurgitation** (Colao *et al*)
- Treatment with cabergoline associated with
  - Increased prevalence of mild tricuspid- and mild pulmonary valve regurgitation (Wakil *et al*)
  - Increased prevalence of aortic valve calcification and mild pulmonary valve regurgitation (Kars *et al*)
  - Greater mitral valve tenting area (Lancelotti *et al*)
  - Higher prevalence of mild tricuspid valve regurgitation in women (Nachtigall *et al*)

## Two studies presented as abstracts at The Endocrine Society Congress 2008, San Fransisco, USA

- **Long-term cabergoline therapy and prevalence of valvular heart disease in patients with prolactinomas; preliminary results from a prospective multicenter study. Delorme S *et al.* (P3-747)**

33 patients (cumulative dose 25-1248 mg), 50 controls referred to echocardiography for various reasons

Clinically significant valvular regurgitation was not increased in patients vs. controls; (n=2 (6%) vs. n=1 (2%), p=0.33)

- **The prevalence of valvular heart disease in a cohort of patients taking Cabergoline for the management of hyperprolactinemia. Devin JK *et al.* (P3-748) *publ Endocrine practice, sept 2008***

Retrospective review. 45 patients (mean dose cabergoline 0.91 ( $\pm$ 0.96) mg/week, mean treatment duration 39 ( $\pm$ 29) months)

Echocardiographic abnormalities were present in 3 patients (6.7%)