Withdrawal of Medical Therapy in Prolactinomas

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THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

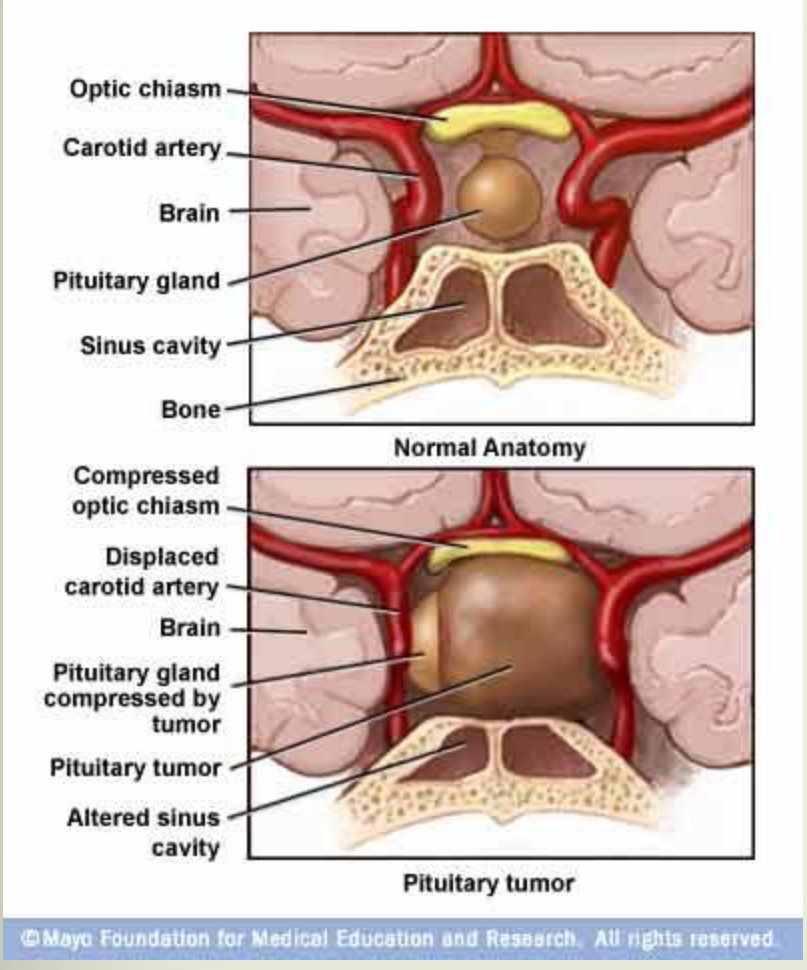
Goals of This Presentation

- Discuss section 4 of the recent Endocrine Society Guidelines: Diagnosis and Treatment of Hyperprolactinemia, February 2011
- Review controversies regarding the long-term use of cabergoline in prolactinomas and effects on heart valves
- Discuss the potential for successful withdrawal of therapy in prolactinomas
- Present UAB data regarding withdrawal of therapy in macroprolactinomas

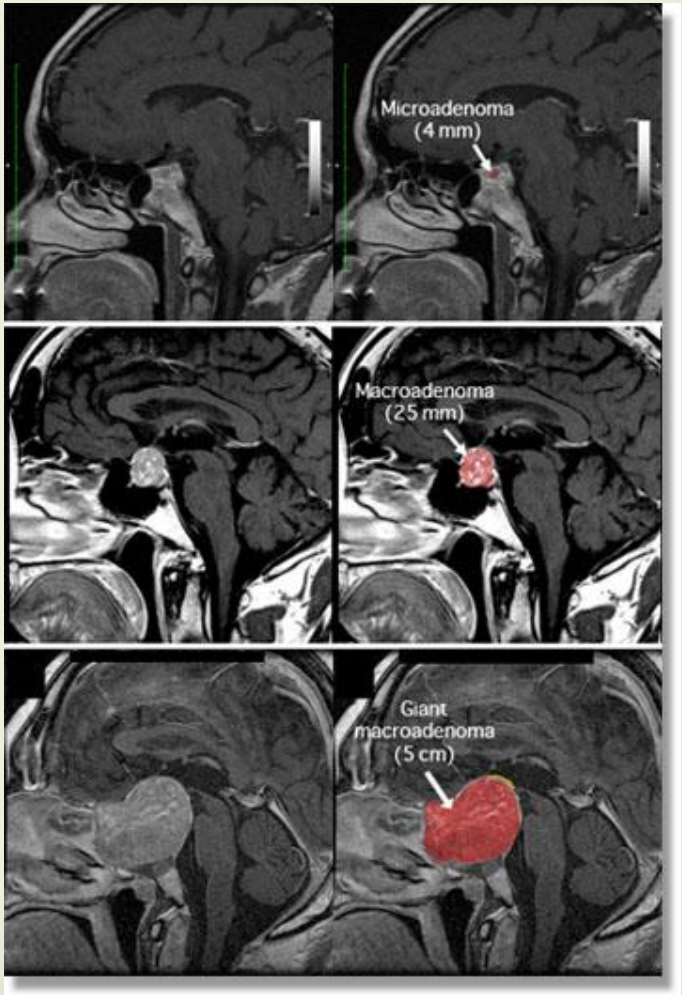
Background

- Microprolactinoma
  - Less than 10 mm
  - Low risk of growth
- Macroprolactinoma
  - Greater than 10 mm
- Malignant Prolactinoma
  - Very rare
  - Defined by metastases

Anatomy



Mayo Medical Foundation



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Epidemiology of Prolactinomas

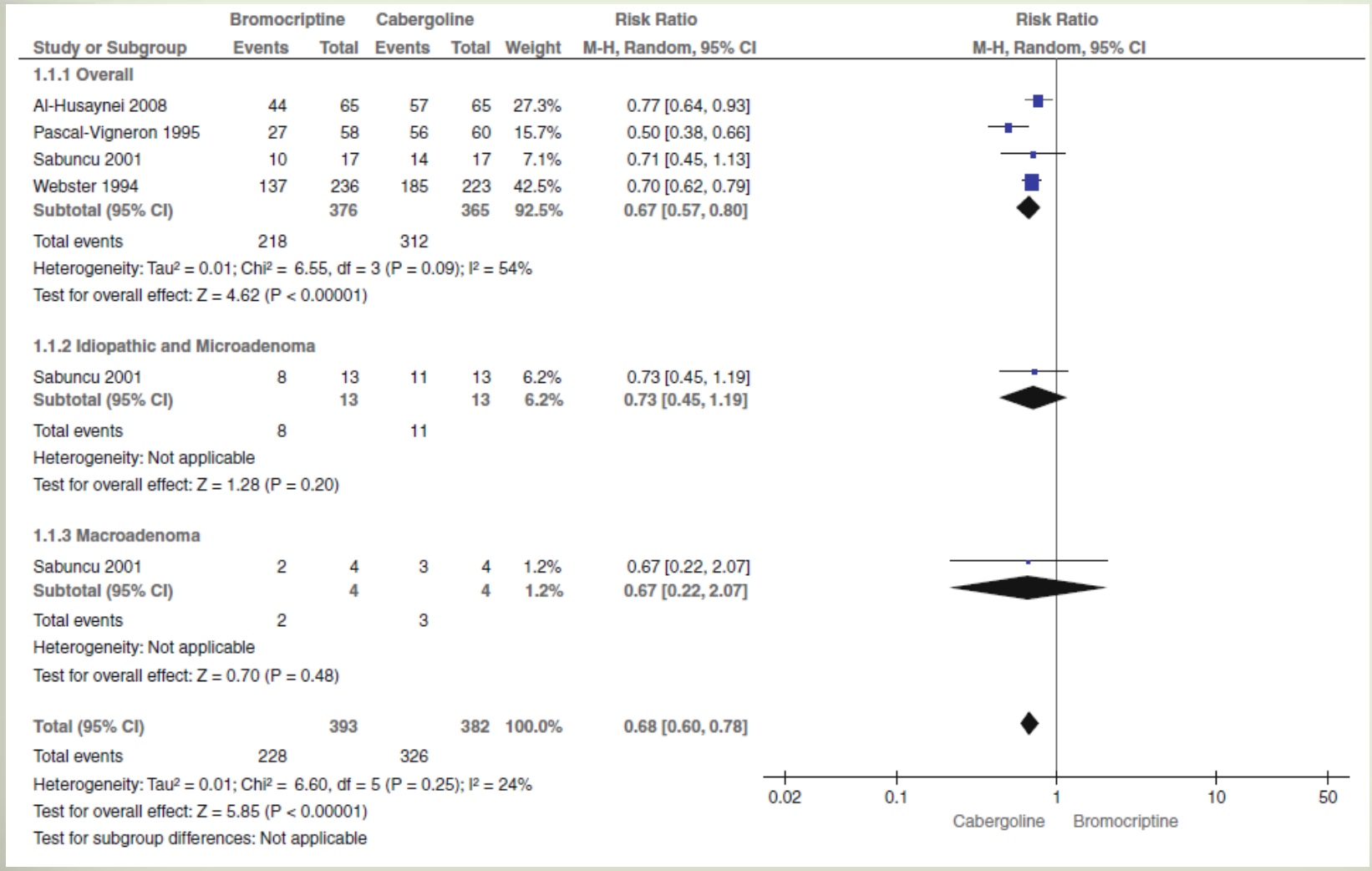
- 40% of all pituitary tumors in adults, 50% of pituitary tumors in children
- Prevalence of 100 per 1,000,000 adults
- Male:Female ratio 1:10, until the 5th decade of life when ratio becomes close to 1:1
- Natural history: Spontaneous regression seen in 32-55% of cases (mostly microadenomas)
- Monoclonal proliferation of lactotrophs

Mancini T, et al. “Hyperprolactinemia and Prolactinomas.” Endocrinol Metab Clin North Am 2008; 37:67-99

Endocrine Society Clinical Practice Guidelines, February 2011

4.1. We recommend dopamine agonist therapy to lower prolactin levels, decrease tumor size, and restore gonadal function for patients harboring symptomatic prolactin-secreting microadenomas or macroadenomas (1 | ⊕⊕⊕⊕). We recommend using cabergoline in preference to other dopamine agonists because it has higher efficacy in normalizing prolactin levels, as well as a higher frequency of pituitary tumor shrinkage (1 | ⊕⊕⊕⊕).

Cabergoline vs. Bromocriptine: Normalization of Prolactin



Study or Subgroup	Bromocriptine Events	Bromocriptine Total	Cabergoline Events	Cabergoline Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Overall						
Al-Husaynei 2008	44	65	57	65	27.3%	0.77 [0.64, 0.93]
Pascal-Vigneron 1995	27	58	56	60	15.7%	0.50 [0.38, 0.66]
Sabuncu 2001	10	17	14	17	7.1%	0.71 [0.45, 1.13]
Webster 1994	137	236	185	223	42.5%	0.70 [0.62, 0.79]
Subtotal (95% CI)		**376**		**365**	**92.5%**	**0.67 [0.57, 0.80]**
Total events	218		312			
Heterogeneity: Tau² = 0.01; Chi² = 6.55, df = 3 (P = 0.09); I² = 54%						
Test for overall effect: Z = 4.62 (P < 0.00001)						
1.1.2 Idiopathic and Microadenoma						
Sabuncu 2001	8	13	11	13	6.2%	0.73 [0.45, 1.19]
Subtotal (95% CI)		**13**		**13**	**6.2%**	**0.73 [0.45, 1.19]**
Total events	8		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.28 (P = 0.20)						
1.1.3 Macroadenoma						
Sabuncu 2001	2	4	3	4	1.2%	0.67 [0.22, 2.07]
Subtotal (95% CI)		**4**		**4**	**1.2%**	**0.67 [0.22, 2.07]**
Total events	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
Total (95% CI)		**393**		**382**	**100.0%**	**0.68 [0.60, 0.78]**
Total events	228		326			
Heterogeneity: Tau² = 0.01; Chi² = 6.60, df = 5 (P = 0.25); I² = 24%						
Test for overall effect: Z = 5.85 (P < 0.00001)						
Test for subgroup differences: Not applicable						

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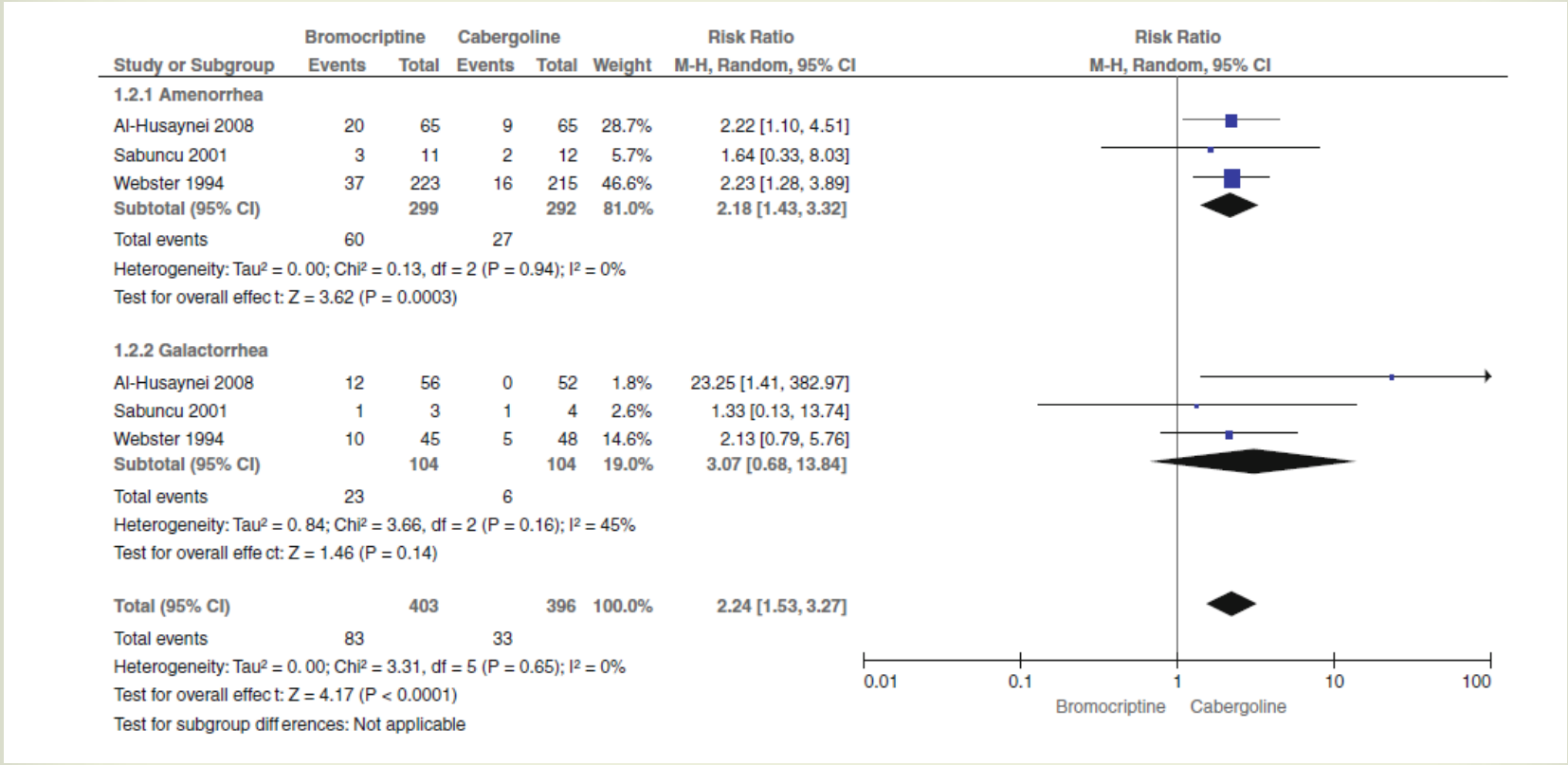
Dos Santos Nunes. Cabergoline vs. Bromocriptine in the Treatment of Hyperprolactinemia. Pituitary, Jan 8. 2011

Cabergoline vs. Bromocriptine: Improvement in Amenorrhea and Galactorrhea



Study or Subgroup	Bromocriptine Events	Total	Cabergoline Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Amenorrhea						
Al-Husaynei 2008	20	65	9	65	28.7%	2.22 [1.10, 4.51]
Sabuncu 2001	3	11	2	12	5.7%	1.64 [0.33, 8.03]
Webster 1994	37	223	16	215	46.6%	2.23 [1.28, 3.89]
Subtotal (95% CI)		**299**		**292**	**81.0%**	**2.18 [1.43, 3.32]**
Total events	60		27			
Heterogeneity: Tau² = 0. 00; Chi² = 0.13, df = 2 (P = 0.94); I² = 0%						
Test for overall effec t: Z = 3.62 (P = 0.0003)						
1.2.2 Galactorrhea						
Al-Husaynei 2008	12	56	0	52	1.8%	23.25 [1.41, 382.97]
Sabuncu 2001	1	3	1	4	2.6%	1.33 [0.13, 13.74]
Webster 1994	10	45	5	48	14.6%	2.13 [0.79, 5.76]
Subtotal (95% CI)		**104**		**104**	**19.0%**	**3.07 [0.68, 13.84]**
Total events	23		6			
Heterogeneity: Tau² = 0. 84; Chi² = 3.66, df = 2 (P = 0.16); I² = 45%						
Test for overall effe ct: Z = 1.46 (P = 0.14)						
Total (95% CI)		**403**		**396**	**100.0%**	**2.24 [1.53, 3.27]**
Total events	83		33			
Heterogeneity: Tau² = 0. 00; Chi² = 3.31, df = 5 (P = 0.65); I² = 0%						
Test for overall effec t: Z = 4.17 (P < 0.0001)						
Test for subgroup diff erences: Not applicable						

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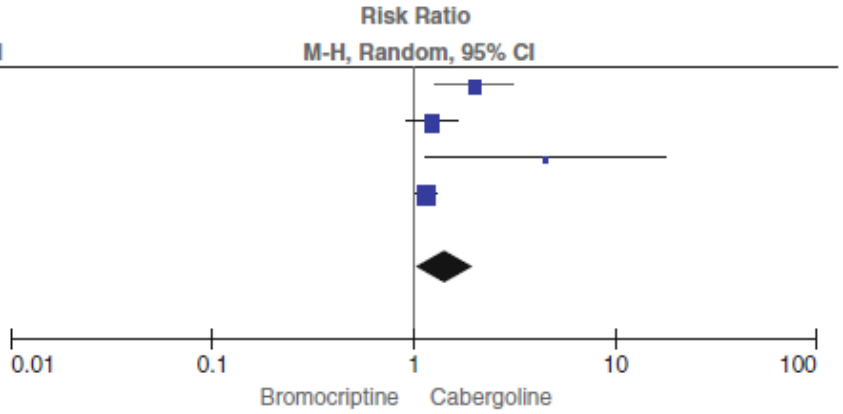
Dos Santos Nunes. Cabergoline vs. Bromocriptine in the Treatment of Hyperprolactinemia. Pituitary, Jan 8. 2011

Cabergoline Vs. Bromocriptine: Adverse Events

Study or Subgroup	Bromocriptine Events	Bromocriptine Total	Cabergoline Events	Cabergoline Total	Weight	Risk Ratio M-H, Random, 95% CI
Al-Husaynei 2008	36	65	18	65	23.5%	2.00 [1.28, 3.13]
Pascal-Vigneron 1995	38	58	32	60	31.2%	1.23 [0.91, 1.66]
Sabuncu 2001	9	17	2	17	5.0%	4.50 [1.14, 17.83]
Webster 1994	167	214	150	221	40.3%	1.15 [1.02, 1.29]
Total (95% CI)		**354**		**363**	**100.0%**	**1.43 [1.03, 1.98]**
Total events	250		202			

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 10.16$, df = 3 (P = 0.02); $I^2 = 70\%$

Test for overall effect: Z = 2.15 (P = 0.03)



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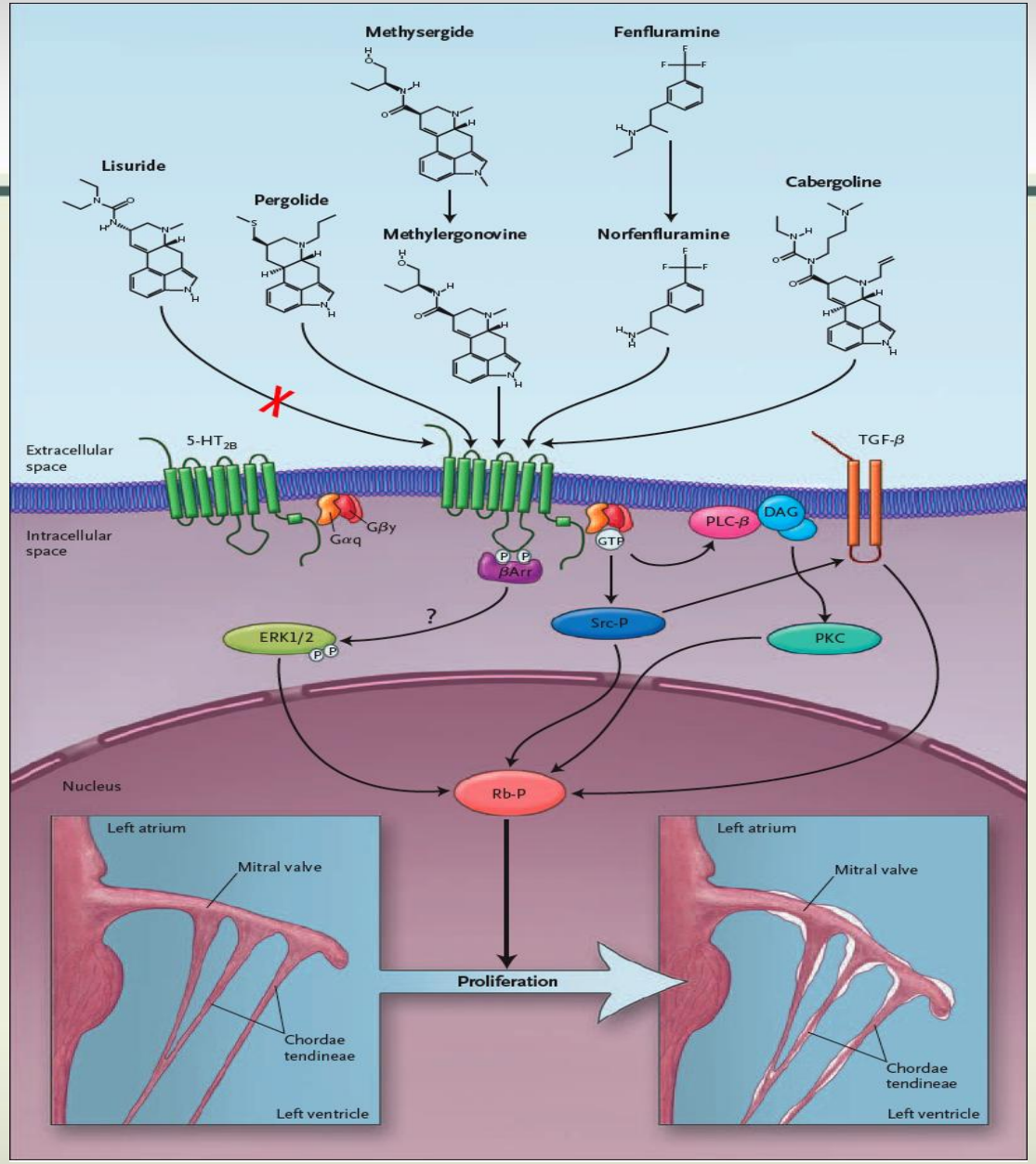
Dos Santos Nunes. Cabergoline vs. Bromocriptine in the Treatment of Hyperprolactinemia. Pituitary, Jan 8. 2011

The Ergot Derivatives

- A large class of drugs
- Cabergoline, pergolide, bromocriptine, quinagolide
- Includes migraine drugs: ergotamine, methysergide
- Valve problems have similarities to carcinoid-related valvulopathies
- Have 5-HT_{2B} activity like other classes (amphetamine derivatives: phen/fen)
- Bromocriptine has limited affinity
- Problems with these drugs predicted before they were reported

The Ergot Derivatives

- Likely due to 5-HT_{2B} agonist activity on serotinergic receptors on exposed heart valves
- Well established now in many of these drugs
- Risk is dose-dependent most likely, but “safe” dose is not clear
- Appears to activate mitogenesis in normally quiescent cells in valves
- Via the Src kinase pathway



Roth B. Drugs and Valvular Heart Disease. New Eng J Med: 356;1:6-9.

2004: Lancet

- 78 patients with Parkinson's disease treated with pergolide
- 18 patients with Parkinson's of similar age and other characteristics never treated with pergolide or any ergot-derived dopamine agonist
- Prevalence of any restrictive valvular disease was 33% in treated group, 0% in controls
- "Important" disease 19% vs 0%
- May be a degree of reversibility

Van Camp et al. Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease. Lancet: 363;1179-1183.

2007: Valvular Heart Disease and Dopamine Agonists for Parkinson's

- Prevalence study
- 155 patients on dopamine agonists for Parkinson's
- Pergolide, cabergoline, and non-ergot derived agonists
- 90 controls
- One of two articles published in the same issue of NEJM

Zanettini et al. Valvular Heart Disease and the Use of Dopamine Agonists for Parkinson's Disease. N Eng J Med 356;1: 39-46.

2007: Valvular Heart Disease and Dopamine Agonists for Parkinson's

- Clinically important regurgitation (moderate to severe/ grade 3 or 4) found in 23.6% of patients on pergolide and 28.6% on cabergoline
- 0 patients on non-ergot derived dopamine agonists (pramiprexole or ropinirole)
- 5.6% in controls
- Average dose of cabergoline 3.6 +/- 2.1 mg per day

Zanettini et al. Valvular Heart Disease and the Use of Dopamine Agonists for Parkinson's Disease. N Eng J Med 356;1: 39-46.

2007: Valvular Heart Disease and Dopamine Agonists for Parkinson's

- Relative risk for significant regurgitation for cabergoline:
  - 4.6 for mitral (P=0.09)
  - 7.3 for aortic (P=<.001)
  - 5.5 for tricuspid (P=0.12)

Zanettini et al. Valvular Heart Disease and the Use of Dopamine Agonists for Parkinson's Disease. N Eng J Med 356;1: 39-46.

Example of Technique

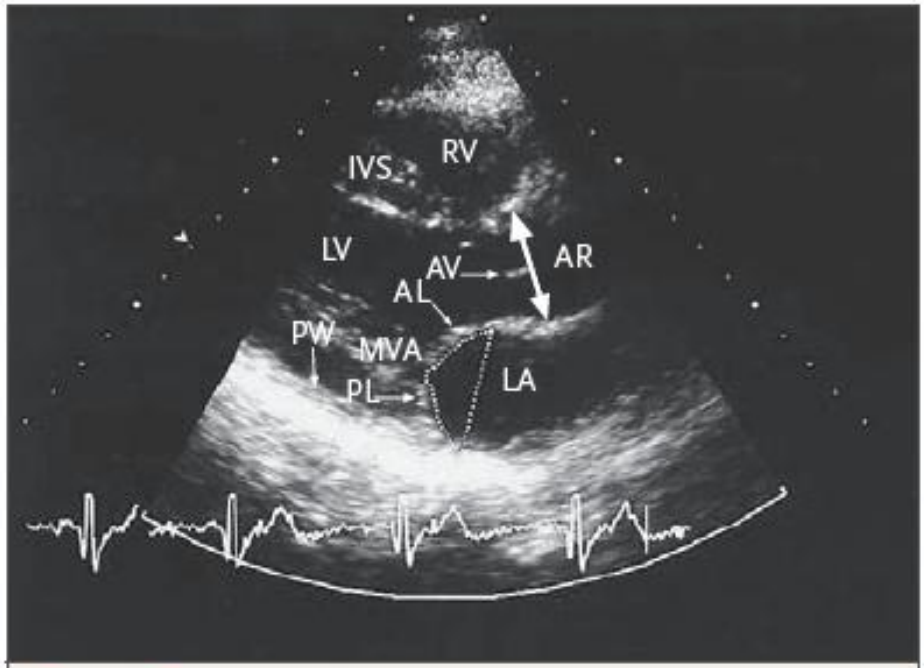


Figure 1. Mitral Tenting Area.

The mitral tenting area (dotted triangle) is shown from the parasternal long-axis view at end systole. The double-headed arrow shows the aortic root (AR). AL denotes anterior mitral leaflet, AV aortic valve, IVS interventricular septum, PW posterior wall, LA left atrium, LV left ventricle, MVA mitral-valve apparatus, PL posterior mitral leaflet, and RV right ventricle.

Zanettiini et al. Valvular Heart Disease and the Use of Dopamine Agonists for Parkinson's Disease. N Eng J Med 356;1: 39-46.

Table 2. Valvular Abnormalities in the Groups of Patients and in the Control Group.*

Variable	Pergolide Group (N=64)	Cabergoline Group (N=49)	Group Receiving Non–Ergot-Derived Dopamine Agonists (N=42)	Control Group (N=90)
Grade of mitral regurgitation — no. of patients (%)				
0 to 1	19 (30)	11 (22)	26 (62)	48 (53)
2	36 (56)	33 (67)	16 (38)	40 (44)
3	6 (9)	4 (8)	0	2 (2)
4	3 (5)	1 (2)	0	0
P value	<0.001	<0.001	0.27	
Grade of aortic regurgitation — no. of patients (%)				
0 to 1	34 (53)	22 (45)	31 (74)	66 (73)
2	21 (33)	15 (31)	11 (26)	21 (23)
3	8 (12)	12 (24)	0	3 (3)
4	1 (2)	0	0	0
P value	0.02	<0.001	0.68	
Grade of tricuspid regurgitation — no. of patients (%)				
0 to 1	17 (27)	8 (16)	23 (55)	47 (52)
2	43 (67)	38 (78)	19 (45)	42 (47)
3	4 (6)	2 (4)	0	1 (1)
4	0	1 (2)	0	0
P value	0.002	<0.001	0.70	
Any grade 3 to 4 regurgitation — no. of patients (%)	15 (23)	14 (29)	0	5 (6)
P value	0.001	<0.001	0.17	
Composite regurgitation score	4.8±2.01	5.14±1.84	3.4±1.29	3.27±2.02
P value	<0.001	<0.001	0.44	
Leaflet thickening of any valve — no. of patients (%)	17 (27)	8 (16)	0	0
P value	<0.001	<0.001		
Mitral-valve tenting area — cm^2	2.95±0.81	3.1±0.80	2.8±0.62	2.37±0.49
P value	0.001	<0.001	0.002	

* Plus–minus values are means ±SD. Regurgitation grades are as follows: 0, absent; 1, trace; 2, mild; 3, moderate; and 4, severe. P values were obtained by Student's t-test and chi-square test for the comparison between each patient group and the control group, and by the chi-square test for trend where applicable.

Zanettiini et al. Valvular Heart Disease and the Use of Dopamine Agonists for Parkinson's Disease. N Eng J Med 356;1: 39-46.

Dose Relationship

Table 3. Regurgitation Grade for Any Valve and Mean Cumulative Dose of Ergot-Derived Dopamine Agonist.

Grade	Pergolide	Cabergoline
	cumulative dose (mg)	
0 to 2	4566±2700	2341±2039
3 to 4	6498±2624	4015±3208
P value*	0.02	0.03

* Regurgitation grades are as follows: 0, absent; 1, trace; 2, mild; 3, moderate; and 4, severe. P values were obtained by Student's t-test for the comparison of different grades of valve regurgitation (0 to 2 vs. 3 to 4) within each group of patients.

Zanettini et al. Valvular Heart Disease and the Use of Dopamine Agonists for Parkinson's Disease. N Eng J Med 356;1: 39-46.

Results

RESULTS

Clinically important regurgitation (moderate to severe, grade 3 to 4) in any valve was found with significantly greater frequency in patients taking pergolide (23.4%) or cabergoline (28.6%) but not in patients taking non–ergot-derived dopamine agonists (0%), as compared with control subjects (5.6%). The relative risk for moderate or severe valve regurgitation in the pergolide group was 6.3 for mitral regurgitation ($P=0.008$), 4.2 for aortic regurgitation ($P=0.01$), and 5.6 for tricuspid regurgitation ($P=0.16$); corresponding relative risks in the cabergoline group were 4.6 ($P=0.09$), 7.3 ($P<0.001$), and 5.5 ($P=0.12$). The mean mitral tenting area was significantly greater in ergot-treated patients and showed a linear relationship with the severity of mitral regurgitation. Patients treated with ergot derivatives who had grade 3 to 4 regurgitation of any valve had received a significantly higher mean cumulative dose of pergolide or cabergoline than had patients with lower grades.

Zanettini et al. Valvular Heart Disease and the Use of Dopamine Agonists for Parkinson's Disease. N Eng J Med 356;1: 39-46.

Dopamine Agonists and Heart Valve Regurgitation

- Huge database study
- UK General Practice Research Database
- Nested Case Control
- 11,417 subjects 40-80 yo given any anti-Parkinson's drugs (of any kind, not all dopamine agonists)
- Cases with new-onset cardiac valve regurgitation matched with 25 control subjects from the cohort
- Incidence-rate ratios calculated for valve regurgitation with the use of different dopamine agonists estimated by logistic-regression analysis

Schade et al. Dopamine Agonists and the Risk of Cardiac-Valve Regurgitation. N Eng J Med 356:1: 39-38.

Table 2. Characteristics of 31 Case Patients with Cardiac-Valve Regurgitation, According to Use of a Dopamine Agonist.*

Characteristic	Pergolide (N=6)	Cabergoline (N=6)	No Dopamine Agonist (N=19)
		no. of patients (%)	
Confirmation of diagnosis			
Echocardiography	2	4	9
Heart catheterization	1	0	0
Clinical information†	3	2	10
Valvular regurgitation‡			
Mitral	4 (67)	5 (83)	17 (89)
Aortic	3 (50)	5 (83)	4 (21)
Tricuspid	0	3 (50)	0
No. of valves involved			
1	5 (83)	1 (17)	17 (89)
2	1 (17)	3 (50)	2 (11)
3	0	2 (33)	0
Clinical symptoms§			
Dyspnea, edema, or both	4	4	12
Syncope, arrhythmia, or chest pain	0	2	1
Unknown	2	0	6

* Among all case patients taking pergolide or cabergoline, the duration of the last prescription overlapped the index date.
† The clinical diagnosis of valvular regurgitation was based on a clinical finding of a typical cardiac murmur, a referral from a physician, or hospitalization for further evaluation of a recent onset of symptoms (e.g., dyspnea or edema).
‡ Percentages may exceed 100 because of overlap between the categories.
§ The symptoms included in this category were those occurring within 18 months before diagnosis.

Schade et al. Dopamine Agonists and the Risk of Cardiac-Valve Regurgitation. N End J Med 356:1: 39-38.

Incidence-Rate Ratio

Table 3. Current Use of Dopamine Agonists and the Risk of Cardiac-Valve Regurgitation.

Exposure	Case Patients (N=31)	Controls (N=663)	Adjusted Incidence-Rate Ratio (95% CI)*
	no. (%)		
No current or recent use of a dopamine agonist†	19 (61)	530 (80)	1.0
Bromocriptine	0	19 (3)	
Cabergoline	6 (19)	34 (5)	4.9 (1.5–15.6)
Pergolide	6 (19)	26 (4)	7.1 (2.3–22.3)
Lisuride	0	1 (0)	
Pramipexole	0	23 (3)	
Ropinirole	0	23 (3)	

* The incidence-rate ratio was adjusted for the use of other dopamine agonists or amantadine.
† This is the reference category, defined as no use of a dopamine agonist during the 12 months before the index date.

Schade et al. Dopamine Agonists and the Risk of Cardiac-Valve Regurgitation. N End J Med 356:1: 39-38.

Table 4. Influence of the Daily Dose of Pergolide or Cabergoline and the Cumulative Duration of Use on the Risk of Cardiac-Valve Regurgitation.

Exposure	Case Patients (N=31)	Controls (N=663)	Adjusted Incidence-Rate Ratio (95% CI)*	P Value†
	no. (%)			
No current or recent use of a dopamine agonist‡	19 (61)	530 (80)	1	
Last daily dose				
Pergolide				0.07
≤3 mg	3 (10)	21 (3)	5.1 (1.3–20.4)	
>3 mg	3 (10)	5 (1)	37.1 (5.1–270.6)	
Cabergoline				0.01
≤3 mg	2 (7)	31 (5)	2.6 (0.5–12.8)	
>3 mg	4 (13)	3 (0)	50.3 (6.6–381.4)	
Cumulative duration of use				
Pergolide				
<6 mo	0	4 (1)		
≥6 mo	6 (19)	22 (3)	9.8 (2.9–33.1)	
Cabergoline				
<6 mo	0	11 (2)		
≥6 mo	6 (19)	23 (4)	7.8 (2.2–27.4)	

* The incidence-rate ratio was adjusted for the use of other dopamine agonists or amantadine.
† P values are for the comparison of the incidence-rate ratios of valvular regurgitation between the higher dose and lower dose of each drug.
‡ This is the reference category, defined as no use of a dopamine agonist during the 12 months before the index date.

Schade et al. Dopamine Agonists and the Risk of Cardiac-Valve Regurgitation. N Eng J Med 356:1: 39-38.

January 9, 2007

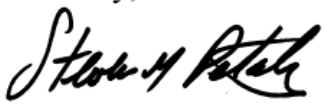
To: AACE Membership

Subject: AACE Alert on Prescribing cabergoline and pergolide

The New England Journal of Medicine published two articles and an editorial concerning the relationship between dopamine agonists and the risks of heart valve disease in the January 4th 2007 edition. These were European studies and the vast majority of the patients had Parkinson's Disease and were taking much higher doses of these agents than would typically be required for treatment of hyperprolactinemia. The first article by Rene Schade et al demonstrates an association between the use of pergolide or cabergoline and valvular heart disease. There was no association noted with cabergoline doses under 3 mg per day and no association with other dopamine agonists, such as bromocriptine. In the second article by Renzo Zanettini et al, the study was limited to patients with Parkinson's disease with average daily dosing of about 3.6 mg daily in the cabergoline group and 2.8 mg in the pergolide group. The groups were not divided out by daily dose in this study.

For patients with prolactin disorders, the use of bromocriptine and typical doses of cabergoline that fall below 3 mg per day do not appear to be associated with an increased risk of valvular disease. It would be prudent to discuss these issues with patients and evaluate those patients that may be at particular risk for valvular disease. AACE will continue to monitor the situation and update you as more information becomes available.

Sincerely,



Steven M. Petak, MD, JD, FACE, FCLM
President, American Association of Clinical Endocrinologists

European Equivalent of FDA

European Medicines Agency
Press office

London, 26 June 2008
Doc. Ref. EMEA/CHMP/322395/2008

PRESS RELEASE
EMEA recommends new warnings and contraindications for ergot-derived dopamine agonists

European Equivalent of FDA

As the risk of fibrosis is not equally established for all ergot-derived dopamine agonists, the CHMP recommended updating their prescribing information as follows:

- For cabergoline and pergolide, for which the prescribing information currently includes a contraindication for patients with evidence of valve problems and a restriction to second-line use in patients with Parkinson's disease:
  - a warning stating that patients must be monitored for signs of fibrosis with echocardiography before treatment is started and regularly during treatment;
  - a reduction of the maximum recommended dose to 3 mg per day;
  - inclusion of cardiac fibrosis as a very common side effect.

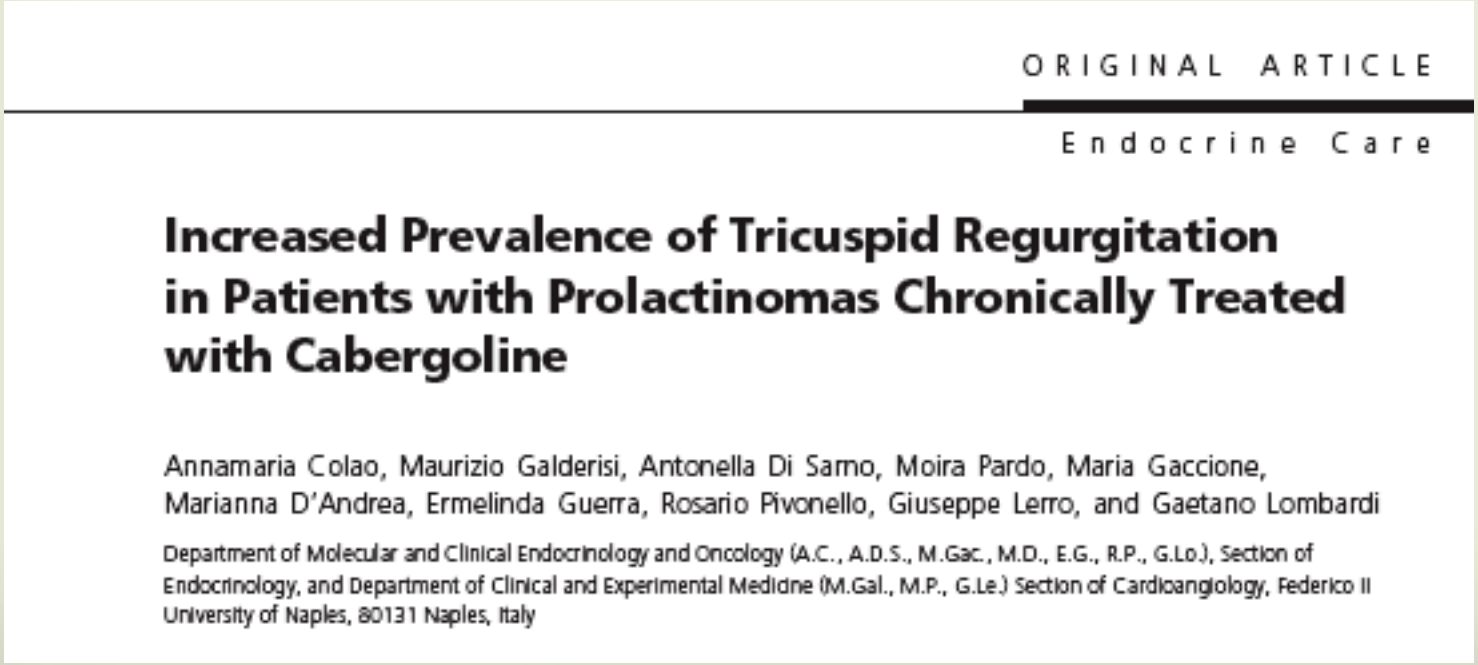
- For bromocriptine and dihydroergocryptine:
  - a contraindication for patients with pre-existing valve problems.

- For bromocriptine:
  - restriction of the maximum dose to 30 mg per day.

- For bromocriptine, dihydroergocryptine and lisuride:
  - a warning on the possible risk of fibrosis in patients taking these medicines at high doses for long periods.

October 2008

- A few small articles had been published showing no association in typical doses used for prolactinomas (0.5-4mg per week)



ORIGINAL ARTICLE

Endocrine Care

Increased Prevalence of Tricuspid Regurgitation in Patients with Prolactinomas Chronically Treated with Cabergoline

Annamaria Colao, Maurizio Galderisi, Antonella Di Sarno, Moira Pardo, Maria Gaccione, Marianna D'Andrea, Ermelinda Guerra, Rosario Pivonello, Giuseppe Lerro, and Gaetano Lombardi

Department of Molecular and Clinical Endocrinology and Oncology (A.C., A.D.S., M.Gac., M.D., E.G., R.P., G.Lo.), Section of Endocrinology, and Department of Clinical and Experimental Medicine (M.Gal., M.P., G.Le.) Section of Cardioangiology, Federico II University of Naples, 80131 Naples, Italy

JCEM Article

- Primary article of concern for endocrinologists
- The only article to implicate cabergoline in doses typical for prolactinomas
- Deserves close scrutiny
- Is an observational, case-control study
- 50 patients treated with cabergoline and 50 age and sex-matched controls
- 20 de novo patients

Calao et al. Increased Prevalence of Tricuspid Regurgitation in Patients with Prolactinomas Chronically Treated with Cabergoline. JCEM: 93 (10):3777-3784.

TABLE 1. Profile of patients and controls at study entry

	De novo patients	Treated patients	Controls	P^1	P^2
No.	20	50	50	1.0	1.0
Women/men	17/3	44/6	44/6	1.0	1.0
Age (yr)	28.2 ± 8.7	36.5 ± 10.5	36.7 ± 10.4	0.74	0.74
Serum PRL levels at diagnosis (μg/liter)	209 ± 234	629 ± 1357			
In women	188 ± 246	418 ± 981			
In men	325 ± 107[a]	2177 ± 2551[a]			
Microprolactinomas	12 (60)	33 (66)			
Macroprolactinomas	6 (30)	16 (32)			
Nontumor hyperprolactinemia	2 (10)	1 (2)			
Serum PRL levels at study entry (μg/liter)	209 ± 234[b]	19.8 ± 27.9	9.2 ± 3.1	<0.0001	0.18
In women	188 ± 246	17.3 ± 23.9	9.6 ± 3.0	0.037	0.037
In men	325 ± 107	37.9 ± 47.8	6.4 ± 2.1	0.14	0.14
Duration of cabergoline treatment (months)		80.7 ± 37.2			
12–60		16 (32)			
>60		34 (68)			
Last cabergoline dose (mg/week)		1.3 ± 1.3			
<1 mg		22 (44)			
1–3 mg		23 (46)			
<3 mg		5 (10)			
Cumulative cabergoline dose (mg)		413.9 ± 390.4			
BMI (kg/m^2)	22.8 ± 5.0	25.4 ± 5.6[c]	22.1 ± 2.6	0.001	0.002
BMI < 25	12 (60)	34 (70)	43 (84)	0.034	0.057
BMI = 25–30	6 (30)	10 (20)	6 (12)	0.20	0.41
BMI > 30	2 (10)	6 (10)	1 (4)	0.15	0.12

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Calao et al. Increased Prevalence of Tricuspid Regurgitation in Patients with Prolactinomas Chronically Treated with Cabergoline. JCEM: 93 (10):3777-3784.

TABLE 2. Echocardiographic findings in patients and controls

	De novo patients	Treated patients	Controls	P^1	P^2
No.	20	50	50	1.0	1.0
Women/men	17/3	44/6	44/6	1.0	1.0
Systolic blood pressure (mm Hg)	115.2 ± 15.4	124.0 ± 13.8[a]	115.2 ± 14.5	0.005	0.0071
Diastolic blood pressure (mm Hg)	74.0 ± 8.3	77.4 ± 9.4[a]	72.3 ± 8.6	0.018	0.01
No hypertension	14 (70)	35 (70)	39 (78)	0.62	0.37
Pre-hypertension	5 (25)	8 (16)	8 (16)	0.63	1.0
Stage 1 hypertension	1 (5)	7 (14)	3 (6)	0.30	0.32
Heart rate (bpm)	70.6 ± 9.3	74.1 ± 9.3	72.1 ± 9.2	0.31	0.16
LVM index (g/m^2)	59.5 ± 11.6	70.1 ± 17.4[b]	66.4 ± 16.6	0.049	0.46
LV fractional shortening (%)	33.4 ± 5.4	33.6 ± 7.0	33.9 ± 6.1	0.95	0.58
Peak velocity E/A ratio	1.42 ± 0.31	1.37 ± 0.38	1.42 ± 0.27	0.64	0.10
Aortic root diameter (mm/m^2)	2.34 ± 0.36	1.57 ± 0.21	2,66 ± 0.35	0.53	0.53
Left atrial diameter (mm/m^2)	2.34 ± 0.36	2.12 ± 0.24	3,22 ± 0.40	0.0003	0.0003
Isovolumic relaxation time (msec)	69.3 ± 12.4	81.1 ± 12.3	73.6 ± 15.3	0.011	0.011
Total peripheral resistance (mm Hg/liter·min·m^2)	2620 ± 832	2929 ± 805	2773 ± 866	0.75	0.75
Pulmonary pressure (mm Hg)		27.9 ± 6.4	30.1 ± 5.0	0.32	0.32
Mild mitral regurgitation	7 (35)	11 (22)	6 (12)	0.085	0.29
Mild aortic regurgitation	10 (0)	2 (4)	1 (2)	0.59	1.0
Mild tricuspid regurgitation	11 (55)	15 (30)	21 (42)	0.13	0.29
Moderate tricuspid regurgitation	0 (0)	27 (54)	9 (18)	<0.0001	<0.0001
Mild pulmonic regurgitation	4 (20)	6 (12)	3 (6)	0.22	0.48

Calao et al. Increased Prevalence of Tricuspid Regurgitation in Patients with Prolactinomas Chronically Treated with Cabergoline. JCEM: 93 (10):3777-3784.

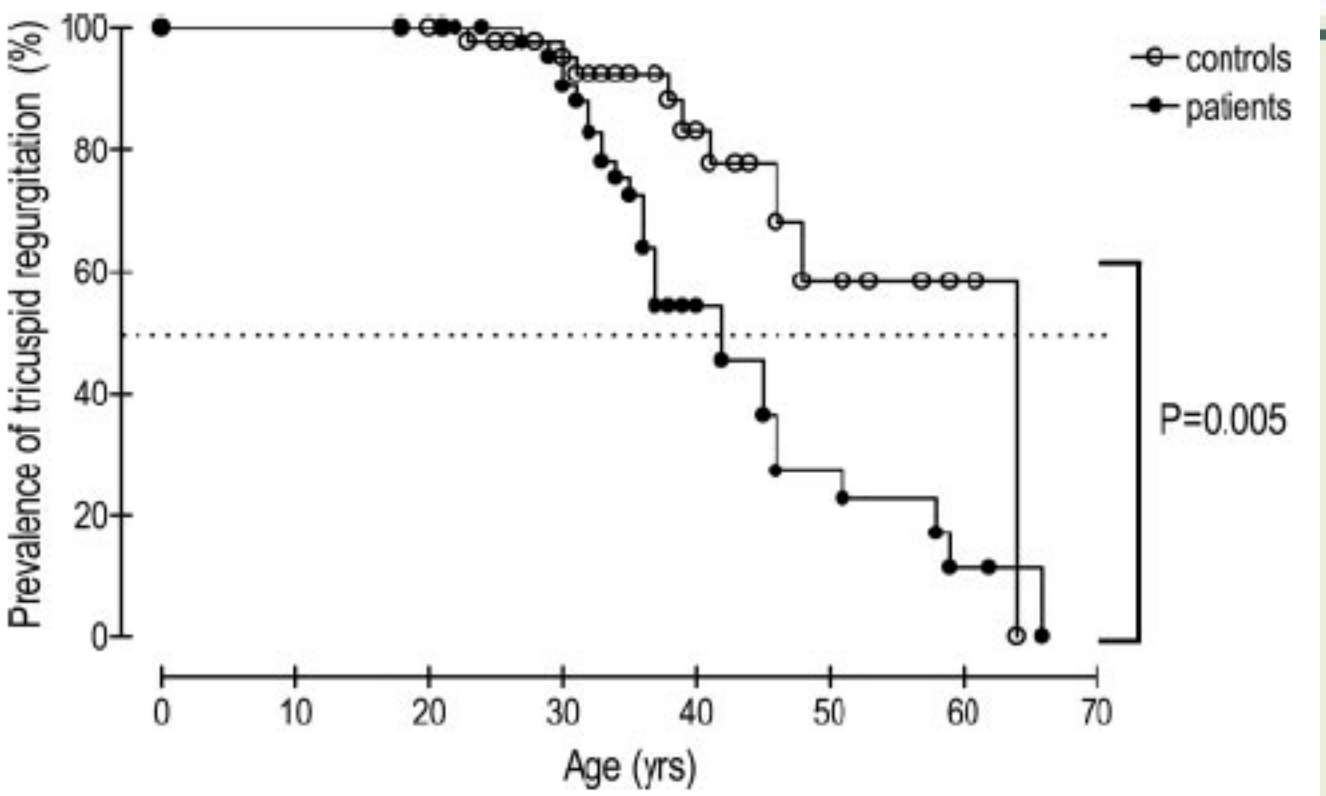

FIG. 1. Kaplan-Meier estimate of age of onset of moderate tricuspid regurgitation in the 50 controls and the 50 patients. The *interrupted line* indicates 50% of the population.

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Calao et al. Increased Prevalence of Tricuspid Regurgitation in Patients with Prolactinomas Chronically Treated with Cabergoline. JCEM: 93 (10):3777-3784.

TABLE 3. Calculation of the relative risk to develop valve regurgitation in patients treated with cabergoline compared with controls

	Relative risk		
	Risk ratio	95% CI	Power 5% significance (%)
Mild mitral regurgitation	1.83	0.76–4.49	18.3
Mild aortic regurgitation	2.0	0.27–15.0	9.0
Mild tricuspid regurgitation	0.71	0.42–1.2	17.7
Moderate tricuspid regurgitation	3.0	1.63–5.77	95.6
Mild pulmonic regurgitation	2.0	0.58–7.02	10.2

Calao et al. Increased Prevalence of Tricuspid Regurgitation in Patients with Prolactinomas Chronically Treated with Cabergoline. JCEM: 93 (10):3777-3784.

TABLE 4. Comparison between patients treated with lower or higher cumulative cabergoline dose according to the median dose of the current population

	Cumulative dose < 280 mg	Cumulative dose > 280 mg	*P*
No.	25	25	
Women/men	24/1	20/5	0.19
Age (yr)	36 ± 12	37 ± 9	0.79
Serum PRL levels at diagnosis (μg/liter)	408 ± 863	850 ± 1706	0.31
Serum PRL levels at study entry (μg/liter)	10.7 ± 14.4	28.9 ± 34.8	0.017
BMI (kg/m^2)	24.7 ± 4.6	26.1 ± 3.4	0.89
Systolic blood pressure (mm Hg)	124.6 ± 14.0	123.4 ± 13.9	0.59
Diastolic blood pressure (mm Hg)	77.3 ± 8.8	77.5 ± 10.2	0.78
LVM index (g/m^2)	68.7 ± 15.8	71.6 ± 19.0	0.51
LV fractional shortening (%)	34.3 ± 8.1	33.0 ± 6.0	0.73
LV internal diastolic diameter (mm/m^2)	2.82 ± 0.24	2.71 ± 0.28	0.13
Peak velocity E/A ratio	1.34 ± 0.40	1.39 ± 0.29	0.35
Deceleration time of E velocity (msec)	179.8 ± 29.9	177.1 ± 22.0	0.77
Aortic root diameter (mm/m^2)	1.57 ± 0.21	1.57 ± 0.21	0.85
Left atrial diameter (mm/m^2)	2.08 ± 0.22	2.16 ± 0.24	0.27
Isovolumic relaxation time (msec)	81.8 ± 9.4	80.5 ± 14.6	0.47
Total peripheral resistance (mm Hg·liter·min·m^2)	2897 ± 792	2962 ± 832	0.58
Pulmonary pressure (mm Hg)	27.9 ± 6.4	27.8 ± 6.5	0.85
Mild mitral regurgitation	6 (24.0)	5 (20.0)	1.0
Mild aortic regurgitation	1 (4.0)	1 (4.0)	1.0
Mild tricuspid regurgitation	11 (40.0)	4 (16.0)	0.064
Moderate tricuspid regurgitation	9 (36.0)	18 (72.0)	0.023
Mild pulmonic regurgitation	3 (12.0)	3 (12.0)	1.0

Data are shown as mean ± SD or prevalence as number of subjects and percentage in parentheses. *P* values refer to the Wilcoxon matched pair test for continuous variables and to the χ^2 test for categorical variables. E, Early; E/A, early/atrial.

2 mg per week x 52 weeks x 3 years= 312 mg

Calao et al. Increased Prevalence of Tricuspid Regurgitation in Patients with Prolactinomas Chronically Treated with Cabergoline. JCEM: 93 (10):3777-3784.

Conclusion: Moderate tricuspid regurgitation is more frequent in patients taking cabergoline (at higher cumulative doses) than in *de novo* patients and control subjects, but the clinical significance of this finding has not been established. A complete echocardiographic assessment is indicated in patients treated long term with cabergoline, particularly in those requiring elevated doses. (*J Clin Endocrinol Metab* 93: 3777–3784, 2008)

Calao et al. Increased Prevalence of Tricuspid Regurgitation in Patients with Prolactinomas Chronically Treated with Cabergoline. JCEM: 93 (10):3777-3784.

Public Health Implications: Mandatory Echocardiography

- Potential for 94,000 new echocardiograms per year in the UK alone
- Prevalence of moderate TR was an “astounding” 27/50 (54%) treated patients
- 9/50 untreated patients (18%)
- Framingham data suggest valvulopathy of mild nature or greater is 19% (MR) and 17% (TR)
- Rates of moderate/severe severity of TR were 0.8%

Sherlock M et al. Dopamine agoinst therapy for hyperprolactinemia and cardiac valve dysfunction: a lot done but much more to do. Heart 2009;95:522-523.

MHRA (UK) Guidelines Issued October 2008

'*Chronic use of ergot-derived dopamine agonists is associated with a risk of fibrosis, particularly cardiac fibrosis. Cardiac valvulopathy should be excluded by echocardiography before treatment with cabergoline or bromocriptine.*' In patients being commenced on cabergoline the update suggests endocrinologists should:

- Monitor patients for signs of cardiac fibrosis during treatment
- Undertake echocardiography within 3–6 months of starting treatment and subsequently at 6–12-month intervals
- Stop treatment if echocardiography shows new or worsened valvular regurgitation, valvular restriction, or valve leaflet thickening
- Exclude pregnancy before administration of cabergoline
- Stop cabergoline in women who are planning a pregnancy one month before trying to conceive.

Subsequently, Pfizer, the manufacturer's of Dostinex (cabergoline) wrote to all endocrinologists stating that among the adverse events seen with cabergoline: '*Very common: cardiac valvulopathy (including regurgitation) and related disorders (pericarditis and pericardial effusion).*'

The Society for Endocrinology

The Society for Endocrinology has not had access to the evidence that underpins these statements and is in contact with the MHRA, European Medicines Agency (EMEA) and Pfizer with the hope of seeing the data on which the Update is based. Until this is achieved it is the Society's position that:

- Dopamine agonists remain the first-line agents for the management of hyperprolactinaemia and a useful adjunct in the management of acromegaly.
- In keeping with good clinical practice, the lowest effective dose of dopamine agonist should be used to achieve the therapeutic goal.
- Patients who are established on a dopamine agonist should continue on their current therapy unless otherwise indicated.
- In keeping with good clinical practice, withdrawal of dopamine agonist should be considered when clinically appropriate.
- Members are encouraged to report any case of fibrotic reaction at any site associated with dopamine agonist therapy to the Committee on Safety of Medicines (CSM) using the established yellow card system.

The Society for Endocrinology

- The Society continues to call for well controlled studies to determine the risk of cardiac valve disease associated with dopamine agonists, particularly cabergoline, in patients being treated for endocrine disorders.
- The Society would welcome detailed studies and analysis on the clinical and health-economic benefits of the intensive cardiac imaging recommended in the MHRA and EMEA guidance.
- Pending the outcome of these studies and/or the emergence of other evidence, the Society recommends that endocrinologists should manage patients receiving cabergoline and bromocriptine in line with the guidance and warnings issued by the British National Formulary (Appendix 2) and MHRA Drug Safety Update (Appendix 1).
- An alternative agent to cabergoline and bromocriptine is quinagolide, a non-ergot derived dopamine agonist, although use of this agent may be associated with neuropsychiatric side effects. Long-term clinical experience with quinagolide is considerably less than with bromocriptine and cabergoline, which makes it difficult to comment on its relative safety over prolonged periods of treatment.

Summary of Data: 2010

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
Colao, 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
Devin, 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
	Group A: 47 treated with cbg	13/34	47 ± 1 (SE)	363 ± 55 (24–1768)	62 ± 5 (12–124)	15% (moderate); 2% (severe)				
	Group B: 31 treated with other DA/surgery									
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).

Valassi et al. Potential Cardiac Valve Effects of Dopamine Agonists in Hyperprolactinemia. JCEM, March 2010.

Where We Stand

- No formal guidelines in US from any organization regarding cardiac echos and cabergoline
- Practice varies widely by institution
- Endocrine Society Guidelines take no formal position
- No further statement from AACE

Withdrawal of Therapy

4.3. We suggest that with careful clinical and biochemical follow-up, therapy may be tapered and perhaps discontinued in patients who have been treated with dopamine agonists for at least 2 yr, who no longer have elevated serum prolactin, and who have no visible tumor remnant on MRI (2 | ⊕○○○).

NEJM, November 2003

Withdrawal of Long-Term Cabergoline Therapy for Tumoral and Nontumoral Hyperprolactinemia

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Paolo Cappabianca, M.D., Carolina Di Somma, M.D., Ph.D.,
Rosario Pivonello, M.D., Ph.D., and Gaetano Lombardi, M.D., Ph.D.

Description of Study

- Observational, prospective study
- All received cabergoline
- Eligibility for withdrawal:
  - Normal PRL level
  - MRI with no tumor or decrease in tumor size
  - >5mm from chiasm and no invasion of critical structures
  - Ability to f/u for at least 24 months
- 354 pts:
  - 57 – stopped Rx because of pregnancy
  - 273 of the remaining 297 – PRL normalized; 200 met eligibility requirements

Coloa et al. Withdrawl of Long-Term Cabergoline Therapy for Tumoral and Non Tumoral Hyperprolactinemia. NEJM, Nov. 20, 2003.

Description of Study

- Verification of prolactinoma:
  - Macro: PRL >200 mcg/L, tumor >10mm
  - Micro: PRL >50 mcg/L, tumor <10mm
  - Nontumoral: PRL > ULN with no other explanation, no tumor visualized
- All patients continued to get CAB for 12 months after determined eligible
- Dose of CAB gradually reduced down to 0.5mg/wk, and if PRL stayed normal, then it was withdrawn
- Definition of recurrence: PRL greater than the upper limit of normal

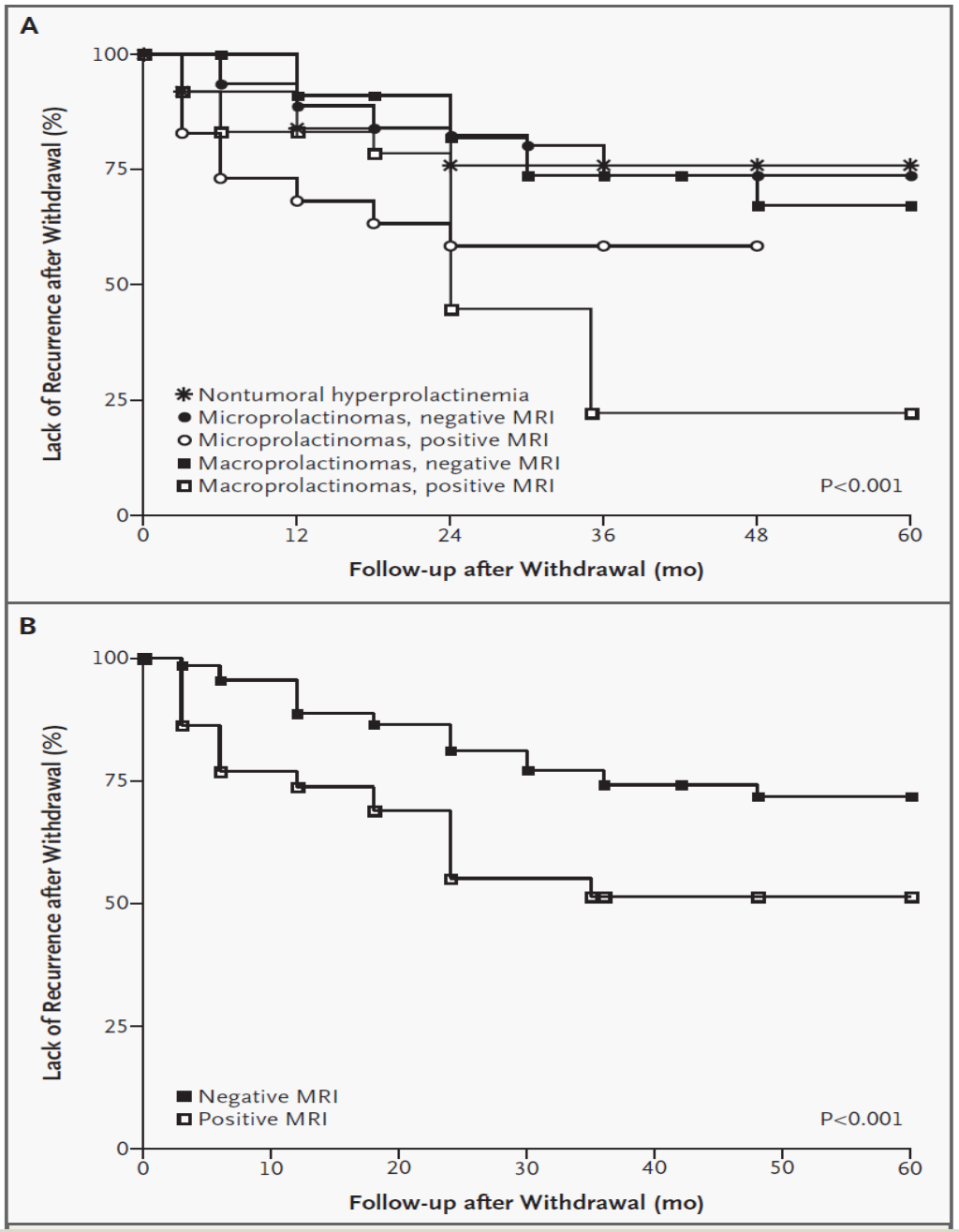
Coloa et al. Withdrawl of Long-Term Cabergoline Therapy for Tumoral and Non Tumoral Hyperprolactinemia. NEJM, Nov. 20, 2003.

Table 2. Characteristics of the Patients According to Whether Hyperprolactinemia Recurred after the Withdrawal of Cabergoline.*

Characteristic	Nontumoral Hyperprolactinemia			Microprolactinomas			Macroprolactinomas		
	Recurrence	No Recurrence	P Value	Recurrence	No Recurrence	P Value	Recurrence	No Recurrence	P Value
Patients — no. (%)	6 (24)	19 (76)		32 (30)	73 (70)		25 (36)	45 (64)	
Sex — no.						0.02			0.74
Female	6	19		25	69		14	23	
Male	0	0		7	4		11	22	
Age — yr									
Range	26–55	18–30	<0.001	19–62	15–66	<0.001	19–70	19–66	0.52
Median	35	28	<0.001	35	28	<0.001	44	50	0.20
Prolactin — μg/liter									
Base line	69.3±5.5	68.3±11.3	0.8	179.3±37.6	154.7±50.6	0.01	935.1±859	904.8±1652	0.93
Nadir with cabergoline	9.8±2.6	1.6±0.8	<0.001	10.1±5.8	4.1±3.6	<0.001	7.3±3.6	4.1±1.9	<0.001
Prolactin suppression — %	85.4±4.6	97.4±0.9	<0.001	94.2±5.0	97.1±5.0	0.005	98.7±1.0	98.9±0.6	0.34
Maximal tumor diameter — mm									
Base line	—	—	—	6.9±1.4	6.8±1.7	0.8	18.4±4.8	16.4±7.1	0.22
Smallest	—	—	—	1.7±1.6	1.0±1.5	0.038	3.7±4.0	1.4±2.5	0.003
Tumor reduction during treatment — %	—	—	—	75.1±23.8	85.2±20.9	0.003	79.9±21.8	90.2±16.6	0.03
Median duration of cabergoline therapy — mo	48	36	0.1	48	36	0.009	48	36	0.01
Maximal dose of cabergoline — mg/wk	0.5±0	0.5±0.2	1	1.6±0.9	1.1±0.6	0.004	1.3±0.4	1.2±0.3	0.19
Average prolactin level at last follow-up visit — μg/liter	44.1±7.0	10.5±4.9	<0.001	48.1±13.1	13.3±4.1	<0.001	54.0±18.4	13.3±4.9	<0.001
Range of follow-up after withdrawal — mo	3–24	24–60	<0.001	3–36	24–60	<0.001	3–30	18–60	<0.001
Median time to recurrence — mo	18	—		12	—		18	—	0.51

* Plus–minus values are means ±SD. P values were calculated with the use of Student's t-test for unpaired (individual) data and the chi-square test or Fisher's exact test for proportions.

Coloa et al. Withdrawl of Long-Term Cabergoline Therapy for Tumoral and Non Tumoral Hyperprolactinemia. NEJM, Nov. 20, 2003.



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Coloa et al. Withdrawl of Long-Term Cabergoline Therapy for Tumoral and Non Tumoral Hyperprolactinemia. NEJM, Nov. 20, 2003.

Study Conclusions

- Nontumoral hyperprolactinemia
  - Median Rx 36 months, median dose 0.5mg/wk
  - 24% recurred but asymptomatic (18 mos), 76% remission (48 mos)
- Microadenomas
  - Median Rx 48 months, median dose 1mg/wk
  - 63/105 – no growth, 42/105 – ~56% decrease in size
  - 30% recurred (12 mos), 70% remission (36 mos)
- Macroadenomas
  - Median Rx 42 months, median dose 1mg/wk
  - 46/70 – no growth, 24/70 – ~61% decrease in size
  - 36% recurred (18 mos), 64% remission (48 mos)

Coloa et al. Withdrawl of Long-Term Cabergoline Therapy for Tumoral and Non Tumoral Hyperprolactinemia. NEJM, Nov. 20, 2003.

JCEM, July 2009

Recurrence of Hyperprolactinemia after Withdrawal of Long-Term Cabergoline Therapy

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Division of Endocrinology and Metabolism (J.K., R.S., G.S.W.), Johns Hopkins University School of Medicine; and Johns Hopkins University School of Public Health (G.Y.), Baltimore, Maryland 21201

Description of Study

- Retrospective study
- All patients on CAB
- 46 patients – no prior surgery or XRT (some had previously been on BCR though)
  - 44 – CAB withdrawn by MD for pregnancy or to check for remission
  - 2 – self-D/C'ed, but still met eligibility requirements
  - 31 micros, 11 macros, 4 non-tumoral
- All patients: CAB at least 23 months with normal PRL, no critical structures involved, no "close proximity" to chiasm
- Median Rx time: 4.3 years
- At time of D/C, 75% on 0.5mg/wk or less
- F/U: Half of pts only followed for <15 months
- Definition of recurrence: Two PRL levels > upper limits of normal

Kharlip et al. Recurrence of Hyperprolactinemia after Withdrawal of Long-Term Cabergoline Therapy. JCEM, July 2009.

TABLE 3. Results of univariate Cox proportional hazard regression models

Predictor	Results of Cox proportional hazard models		
	Estimated hazard ratio	95% CI for hazard ratio	*P* value
Sex			
Male	1.03	0.45, 2.36	0.94
Female (ref.)	1.0		
Age (yr)			
Per 1 yr of age	0.99	0.96, 1.02	0.46
Duration of treatment (months)			
Per month	1.00	0.99, 1.01	0.66
Type of tumor			
Microprolactinoma	0.62	0.18, 2.15	0.45
Macroprolactinoma	0.77	0.19, 3.09	0.71
NTHP (ref.)	1.0		
Prolactin at diagnosis			
Per 1 ng/ml	1.00	1.000, 1.002	0.77
Prolactin nadir			
Per 1 ng/ml	1.08	1.00, 1.18	0.06
Tumor changes on MRI			
Resolved	0.80	0.33, 1.92	0.62
Not resolved (ref.)	1.0		
Maximum tumor size			
Per 1 mm	1.01	0.93, 1.09	0.87
Minimum tumor size			
Per 1 mm	1.18	1.03, 1.35	0.02
Maximum dose of CAB (mg/wk)			0.22
1.5	0.24	0.03, 2.33	0.34
1.0	0.54	0.15, 1.89	0.31
0.5	0.49	0.13, 1.92	
0.25	1.0		
Dose prior to discontinuation (mg/wk)		0.39, 2.92	0.89
1.0 and more	1.07	0.32, 2.14	0.70
0.5	0.83		
0.25	1.0		
Use of bromocriptine		0.62, 3.31	0.41
Yes	1.43		
No	1.0		
Total duration of treatment (including bromocriptine)	1.00	0.99, 1.01	0.90
Use of OCPs during treatment with CAB		0.15, 1.48	0.198
Yes	0.47		
No	1.0		
Use of OCPs after withdrawal of CAB		0.13, 2.59	0.475
Yes	0.58		
No	1.0		
Presence of pituitary deficits at presentation[a]			
Yes	0.94	0.42, 2.11	0.90
No	1.0		

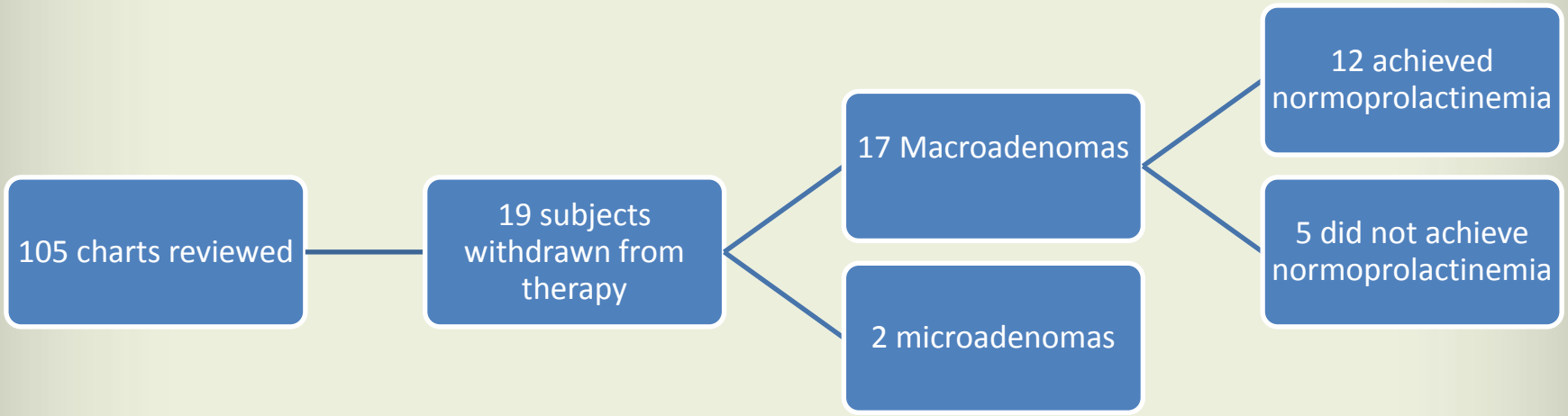
[a] Includes presence of hypogonadism, central hypothyroidism, adrenal insufficiency, GH deficiency, and diabetes insipidus.

Study Conclusions

- Overall rate of recurrence: 54%
  - Did not change with exclusion of the patients who had self-discontinued or had CAB discontinued due to pregnancy
  - Also didn't change with exclusion of patients who had <50% size reduction, tumor reduction in a dimension other than the largest, or those on doses >0.5mg/wk
  - Estimated risk of recurrence at 18 months: 63%
- Predictors of recurrence:
  - Size of tumor at time of withdrawal: each mm of size reduction leads to an 18% decrease in recurrence risk (p=0.02)
  - PRL nadir: each 1ng/mL of PRL leads to an 8% increase in recurrence risk (p=0.062)

Kharlip et al. Recurrence of Hyperprolactinemia after Withdrawal of Long-Term Cabergoline Therapy. JCEM, July 2009.

Study Design: Retrospective Review of UAB Database (Macroadenomas)



Study Design, Retrospective Review of Database

- Recurrence defined as a prolactin level >29.2 ng/dL
- Time to recurrence estimated from time of medication withdrawal to first available elevated prolactin
- Retrospective review: no standardized protocols for deciding to withdraw therapy, timing of withdrawal, or subsequent follow-up
- Non-parametric statistics were used to determine the association between several clinical variables and remission status

Patient Characteristics

- **Sex, n (%)**
  - Females: 2 (16.7)
  - Males: 10 (83.3)
- **Race, n (%)**
  - White: 10 (83.3)
  - African-American: 2 (16.7)
- **Age at diagnosis (yr)**
  - Median: 39
  - Range: 11-63
- **PRL at diagnosis (ng/mL)**
  - Median: 2599.5
  - Range: 168-14,151
  - No. of missing values: 1
- **PRL nadir (ng/mL)**
  - Median: 5.25
  - Range: <0.3-25.8.

Patient Characteristics

- **Maximal tumor diameter at presentation (mm)**
  - Median: 18
  - Range: 10-30
  - No. of missing values: 5
- **Maximal tumor diameter at time of DA withdrawal (mm)**
  - Median: 5
  - Range: 0-21
  - No. of missing values: 1
- **Tumor size change, n (%)**
  - Resolved: 5 (41.7)
  - Decreased size: 3 (25.0)
  - No. of missing values: 4 (33.3)
- **Reduction in tumor size (%)**
  - Median: 100
  - Range: 55.6-100
  - No. of missing values: 5
- **Treatment details** [a]
  - Duration of treatment (years)
  - Median: 12
  - Range: 5-16
  - **Type of DA, n (%)**
  - Bromocriptine: 3 (25)
  - Cabergoline: 3 (25)
  - Combination BCR + CAB: 5 (41.7)
  - Combination BCR + pergolide: 1 (8.3)

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[a] One patient also had surgery and radiation therapy prior to starting DA therapy

	Remission	Recurrence	P Value
• **Sex**			
Male	6	4	0.530
Female	1	1	
• **Race**			
White	6	4	0.530
African-American	1	1	
• **DA initial dose** [a,b]			
Low	3	3	0.364
Medium	7	1	
• **DA maximum dose**			
Low	2	1	0.227
Medium	3	2	
High	2	2	
• **DA dose at withdrawal**			
Low	5	4	0.273
Medium	1	0	
High	0	1	
• **Reason for withdrawal**			
Clinical improvement	6	3	0.106
Self-discontinued	0	2	
Elevated LFTs	1	0	
• **Change in tumor diameter (%)** [c]			
55.6	1	1	0.381
72.2	1	0	
100	3	1	
• **Initial prolactin** [d]			
Elevated	3	1	0.173
Moderately elevated	0	1	
Extremely elevated	3	3	
• **Maximum diameter at withdrawal (mm)**			
Resolved	4	1	0.045
1-5	1	0	
6-10	0	1	
11-15	2	1	
>20	0	1	

[a] Initial dose unknown for 1 subject (recurrence).
[b] Low dose: bromocriptine <10mg/d, cabergoline </= 0.5mg/wk, pergolide
Medium dose: bromocriptine 10-30mg/d, cabergoline 0.6-1.5mg/wk, pergolide
High dose: bromocriptine >30mg/d, cabergoline >1.5mg/wk, pergolide
[c] Change in diameter unable to be calculated for 5 subjects due to initial MRI unavailability (3 recurrence, 2 remission).
[d] Initial prolactin level unknown for 1 subject (remission).

Conclusions

- Remission rate was 58% for macroprolactinomas (vs. 55-64% in other two studies)
- We did reproduce the findings about the significance of a negative MRI
- Endocrine Society Guidelines are appropriately vague at this time

Key References

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