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A follow-up study of the prevalence of valvular heart abnormalities in hyperprolactinemic patients treated with cabergoline

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Key words: cabergoline, hyperprolactinemia, cardiac valvulopathy

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1 **CONTEXT**

2 Uncertainty exists whether the long-term use of ergot-derived dopamine agonist (DA) drugs for
3 the treatment of hyperprolactinemia may be associated with clinically significant valvular heart
4 disease; and whether current regulatory authority guidelines for echocardiographic screening are
5 clinically appropriate.

6 **OBJECTIVE**

7 To provide follow-up echocardiographic data on a previously described cohort of patients treated
8 with DA for lactotrope pituitary tumors; and to explore possible associations between structural
9 and functional valve abnormalities with the cumulative dose of drug used.

10 **DESIGN**

11 Follow-up echocardiographic data were collected from a proportion of our previously reported
12 cohort of patients; all had received continuous DA therapy for at least 2 years in the intervening
13 period. Studies were performed according to British Society of Echocardiography minimum
14 standards for adult transthoracic echocardiography. Generalised estimating equations with
15 backward selection were used to determine odds ratios of valvular heart abnormalities according
16 to tertiles of cumulative cabergoline dose, using the lowest tertile as the reference group.

17 **SETTING**

18 Thirteen centers of secondary/tertiary endocrine care across the United Kingdom.

19 **RESULTS**

20 There were 192 patients (81 males; median age, 51 years; interquartile range [IQR], 42–62).
21 Median (IQR) cumulative cabergoline doses at the first and second echocardiograms were 97mg
22 (20-377) and 232mg (91-551) respectively. Median (IQR) duration of uninterrupted cabergoline
23 therapy between echocardiograms was 34 months (24-42). No associations were observed
24 between cumulative doses of dopamine agonist used and the age-corrected prevalence of any
25 valvular abnormality.

26 **CONCLUSION**

27 This large UK follow-up study does not support a clinically significant association between the
28 use of DA for the treatment of hyperprolactinemia and cardiac valvulopathy.

29

30 **INTRODUCTION**

31 Patients with lactotrope pituitary tumors who require medical therapy are typically treated with
32 dopamine agonists (DAs). Amongst the ergot-derived DAs in common use, cabergoline is most
33 widely prescribed because of its greater efficacy and better side-effect profile than
34 bromocriptine, although some physicians still favor the latter drug for use in women attempting
35 conception and for those in established pregnancy who require treatment to control tumor size.

36 Following the publication of a number of case reports, cohort studies and case-controlled series
37 describing the association of short-term, intensive high dose cabergoline therapy for Parkinson's
38 disease with cardiac valvulopathy^{1,2,2,3}, guidance was issued by various medicines regulatory
39 authorities recommending screening with transthoracic echocardiography (TTE) for all patients
40 with hyperprolactinemic states on maintenance treatment with this class of drug⁴.

41 Since then, a number of groups have contributed data to the literature in order to guide practice
42 in this area. Most studies have reported TTE findings in modest numbers of patients with
43 prolactinomas and compared them with healthy controls^{5-7,7-15}. We have previously reported TTE
44 data from a large (747 patients), multi-center, cross-sectional UK study of patients with
45 hyperprolactinemia treated with DAs¹⁶. Patients were divided into quartiles according to
46 cumulative DA dose, with the lowest quartile acting as the 'reference group' against which
47 higher quartiles of DA 'exposure' were compared¹⁶. Here, longitudinal TTE findings are
48 reported in a proportion of those patients, all of whom had received continuous DA therapy for at
49 least 2 years in the intervening period.

50

51 MATERIALS AND METHODS

52

53 Patients

54 All 28 centers participating in our original study were contacted and invited to contribute data to
55 this follow-up study. Thirteen centers contributed anonymized data from 192 patients (median
56 age, 51 years; interquartile range [IQR], 42–62), of which 81 were males. The remaining fifteen
57 centres cited time and/or local financial resource constraints as the reasons for not participating
58 in this follow-up study. Inclusion criteria for this study were that all patients must have had two
59 TTEs, separated temporally by at least two years and that all patients should have received
60 uninterrupted cabergoline therapy between those two studies. Demographic and clinical data
61 collected previously was cross-checked again for this study, included age, gender, duration of
62 treatment, maintenance dose of drug, whether the tumor was a microadenoma (≤ 10 mm) or
63 macroadenoma (≥ 10 mm), and the presence or absence of any previous cardiac history or risk
64 factors for cardiac disease (smoking, hypertension, diabetes mellitus, hyperlipidemia, history of
65 rheumatic fever). Cumulative doses of cabergoline were calculated by multiplying the weekly
66 dose by the duration of therapy; this calculation was repeated each time the patient's dose was
67 adjusted by the supervising physician and allowed the calculation of a total cumulative
68 cabergoline exposure dose.

69

70 Echocardiography

71 As in our previous study, all TTE examinations were performed by fully-trained sonographers in
72 accordance with the British Society of Echocardiography minimum dataset for a standard adult
73 transthoracic echocardiogram¹⁷. Valve assessment included evaluation of morphology (leaflet
74 thickening, calcification, mobility) and function of the mitral, aortic, pulmonary, and tricuspid
75 valves in multiple views. Two-dimensional imaging was followed by color Doppler
76 echocardiography after optimizing gain (to eliminate random speckle color from non-moving
77 regions) and Nyquist limit (50–60 cm/s)¹⁸. Standard pulse wave and continuous wave Doppler
78 examinations were performed. Valvular regurgitation was quantified as absent, mild, moderate,
79 or severe by integrating multiple indices of severity^{4,19}. As in our previous study, potentially
80 clinically significant valvular disease (morphological or functional) was considered to be
81 moderate or above.

82

83 **Statistical Analysis**

84 TTE parameters were described using medians and IQRs. The Wilcoxon signed rank test was
85 used to compare parameters between the first and second studies. Generalised estimating
86 equations, to take account of the repeated TTE measurements, were used to determine univariate
87 odds ratios (ORs) for moderate or above abnormalities of any valve according to tertiles of
88 cabergoline dose and patient characteristics. Generalised estimating equations with backwards
89 selection were used to determine multivariate ORs. ORs were also calculated for mild or above
90 valvular abnormalities. Statistical significance was taken as $p < 0.05$. All analyses were performed
91 in Stata version 13 (StataCorp, College Station, Texas, USA).

92

93 The project was supported by the Clinical Endocrinology Trust. Institutional review board
94 permission was obtained at each center.

95

96

97 **RESULTS**

98 Of the 192 patients, there were 88 (46%) with a microadenoma, 93 (48) had a macroadenoma
99 and in the remainder it was not specified by the referring physician. Median (IQR) cumulative
100 cabergoline doses at the time of the first and second TTEs were 97mg (20-377) and 232mg (91-
101 551) respectively. Median (IQR) weekly cabergoline dose was 0.5mg (0.5-1.0). Median (IQR)
102 duration of uninterrupted cabergoline therapy between the two studies was 34 months (24-42).

103 There were 11 echocardiographic abnormalities of moderate severity at the time of the first TTE.
104 Of these, 6 had become mild by the time of the second study, 4 were unchanged and in 1 patient
105 moderate tricuspid regurgitation was reported to have progressed to severe. There were 4 mild
106 echocardiographic abnormalities at the first TTE that had become moderate by the time of the
107 second (table 1). More detailed information on the 9 echocardiographic abnormalities of
108 moderate or above severity at the second study (in 7 patients) is also presented in table 1.

109 Calculated ORs of any valvular abnormality (thickening, restricted movement, calcification,
110 stenosis, regurgitation, with and without the inclusion of mild lesions) by tertile of exposure to
111 DA are shown graphically in table 2. No associations were observed between cumulative doses
112 of cabergoline and the age-corrected prevalence of any valvular abnormality. ORs were not
113 influenced by the presence or absence of a cardiac history, previous rheumatic fever or any of the
114 risk factors for heart disease and no differences were observed when patients with micro- and
115 macro-adenomas were analysed separately.

116

117 **DISCUSSION**

118 In this study we have performed detailed, follow-up TTE in a large cohort of patients with
119 hyperprolactinemia who, in addition to being exposed to DA therapy before the first
120 examination, received uninterrupted treatment for at least two years before the second.
121 Compared to our previous report, this cohort of patients contains a greater proportion of men and
122 patients classified as having a macroadenoma. This is likely to reflect the higher background
123 remission rate in women and of microadenomas such that some of these originally reported
124 patients will have discontinued DA at some stage in the intervening period and not have been
125 eligible for inclusion in this study. A patient population enriched with men and patients with
126 macroadenomas is a useful one to study as it contains those most likely to need to continue DA
127 therapy for a prolonged period of time. These data do not suggest a clinically significant effect of
128 DA therapy at ‘endocrine doses’ on cardiac valvular function during medium-term follow-up and
129 provide further reassurance to physicians using this class of drug for this clinical indication.

130

131 The background to the clinical question of the cardiac safety of DA has been extensively
132 documented and summarised. Cabergoline binds to the same receptors (5-HT_{2B}) that mediate
133 carcinoid heart disease, although there is no direct relationship between plasma levels of 5-HT
134 and presence of valvulopathy suggesting that other factors may be required for the pathogenesis
135 of valve dysfunction²⁰. Although cardiac valvulopathy may occur in patients with neurological
136 disorders currently treated with doses of cabergoline up to 3mg daily for more than 6 months¹,
137 many endocrine physicians experienced in the management of pituitary disease were surprised
138 by the various regulatory authority recommendations for TTE surveillance in patients with
139 hyperprolactinemia. The doses involved in the treatment of hyperprolactinemia are, typically,
140 approximately 1/20th – 1/40th of those used in the treatment of Parkinson’s disease. Most
141 lactotrope pituitary microadenomas occur in women, for whom either spontaneous remission or
142 intervening pregnancies dictate that the drug is frequently prescribed for a limited period of time.
143 Even if women require prolonged use of cabergoline for hyperprolactinemia, it is often possible
144 to discontinue therapy at the time of the menopause. Our data suggest that the current
145 recommendations (exclusion of cardiac valvulopathy before commencement of DA therapy;
146 second TTE 3–6 months after starting treatment; and serial examinations at 6- to 12-month

147 intervals while DA therapy is continued) are out of keeping with the risk of developing clinically
148 significant valve disease. Based on estimates of the prevalence of lactotrope pituitary tumors,
149 such a surveillance program would require an estimated 90 000 extra TTEs per year in the
150 United Kingdom¹⁹ at a time when both public and private healthcare providers are seeking to
151 ensure use of cardiovascular imaging is appropriate²¹. Non-financial implications, such as patient
152 anxiety and inconvenience, are harder to quantify.

153

154 The publication of data regarding valvulopathy in patients with Parkinson's¹ came more than two
155 decades after the first clinical trials of DA agonist use in hyperprolactinemia²². There are major
156 problems in designing studies to address the issue of possible cardiac valvulopathy in patients
157 taking 'endocrine doses'. Withholding DA therapy from patients with hyperprolactinemia
158 (particularly women wanting to conceive) in order to perform controlled studies would clearly be
159 unethical; and any postulated cardiac effects of DA therapy (positive or negative) would be hard
160 to separate from any secondary changes that may occur as a consequence of normal gonadal
161 steroid levels being restored to previously hypogonadal patients. Further, with the patent on
162 cabergoline having expired, large-scale multi-center phase IV studies in this area are improbable.
163 Most of the literature in this area therefore comes from single-center studies of modest numbers
164 of DA-treated patients compared to age-matched healthy controls. The majority of those studies
165 have provided reassuring data regarding valve function, with just three reports of increased
166 tricuspid regurgitation (moderate in one, mild in two others) and an inconsistent relationship to
167 the cumulative dose of drug^{5,7,8}

168

169 To our knowledge, this is the largest follow-up echocardiographic study of hyperprolactinemic
170 patients treated with DA. Although the size is an obvious strength, as in our previous study, an
171 obvious weakness is the lack of a true control group, with the lowest tertile of DA exposure
172 serving as our 'surrogate control'. In an earlier follow-up study, statistically significant increases
173 in aortic valve calcification were observed with DA therapy, although these changes did not
174 translate into any alterations in valve function^{7,23}. Moreover, while grading the extent of valve
175 calcification is an important factor in predicting outcome in AS²⁴, visual estimation on 2D

176 echocardiography is subjective and has high inter-observer variability²⁵. This could simply be
177 that cardiac valvulopathy develops over a prolonged time period and that clinically significant
178 functional changes (defined in most studies as moderate severity or above) cannot be detected
179 over the timescales of the reported studies. It was for this reason that we included an analysis
180 based on ‘mild or above severity’ as a statistically significant increase in the prevalence of mild
181 valvular abnormalities could provide preliminary evidence of developing clinically relevant
182 valvulopathy. We found no evidence of an increase in mild anatomical or functional
183 valvulopathy with increasing DA exposure.

184

185 Reassuring group data can sometimes conceal clinically important effects in small numbers of
186 patients. It is for this reason that we present the details of the 9 moderate or above
187 echocardiographic abnormalities in 7 patients seen at the second TTE; these cases illustrate some
188 of the challenges of interpreting echocardiographic findings in this context. The median age of
189 the 7 patients was 74; all except one patient was older than the median age of the overall cohort.
190 Although this may suggest the observed abnormalities were age-related, this group of patients
191 were also heavily exposed to DA; all except one patient had received a cumulative cabergoline
192 dose above the median for the overall cohort. In case 5, for example, whilst the risk factor profile
193 and documented history of IHD may well have been important factors in the progressive mitral
194 regurgitation, the appearance of thickening of the valve leaflets is also compatible with DA
195 therapy being aetiologically contributory. Determining which echocardiographic abnormalities
196 carry clinical significance is also difficult. Current echocardiography systems such as those used
197 in this study detect ‘physiological’ tricuspid regurgitation in almost all subjects and
198 ‘physiological’ mitral regurgitation in more than half²⁶. Whilst ‘trivial’ and ‘mild’ regurgitation
199 are so common, it is also recognised that significant reporter bias exists when information about
200 the use of DA in patients undergoing surveillance TTE is provided to cardiac technicians²⁷.
201 Moreover, quantification, even when using recognised methodology including vena contracta
202 and proximal isovelocity surface area, is only modestly reliable; inter-observer agreement for
203 grading mitral regurgitation as severe or non-severe is only 0.28 between specialists working in
204 academic hospitals²⁸. In patients with less severe regurgitation, not only will inter-observer
205 variability be higher but there may well be physiological variation that will cause some change in

206 categorisation. It is not clear whether newer imaging modalities such as cardiac magnetic
207 resonance imaging will provide more accurate or reproducible assessment of mild degrees of
208 regurgitation²⁹.

209

210 In summary, this follow-up echocardiographic study provides further, reassuring evidence that
211 cardiac valvulopathy is not a major clinical issue in patients with lactotrope pituitary adenomas
212 treated with DA over this timescale. Prospective, case-controlled studies of the size and duration
213 required formally to address this issue are unlikely to be conducted, given their prohibitive cost
214 and logistical challenges. Although the design and duration of the published studies cannot
215 ‘exonerate’ DA of a possible role in causing cardiac valvulopathy, we suggest that the time is
216 now appropriate for regulatory authorities to consider revising the guidelines for surveillance
217 echocardiography in this group of patients.

218

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