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

WM Drake<sup>1</sup>, CE Stiles<sup>1</sup>, JS Bevan<sup>2</sup>, N Karavitaki<sup>3</sup>, PJ Trainer<sup>4</sup>, DA Rees<sup>5</sup>, TI Richardson<sup>6</sup>,  
SE Baldeweg<sup>7</sup>, N Stojanovic<sup>8</sup>, RD Murray<sup>9</sup>, AA Toogood<sup>10</sup>, NM Martin<sup>11</sup>, B Vaidya<sup>12</sup>,  
TS Han<sup>13</sup>, RP Steeds<sup>14</sup>

On behalf of the UK Cabergoline valvulopathy study group\*

\*FC Baldeweg<sup>7</sup>, UE Sheikh<sup>12</sup>, N Kyriakakis<sup>9</sup>, S Parasuraman<sup>2</sup>, L Taylor<sup>14</sup>, N Butt<sup>6</sup>, S Anyiam<sup>4</sup>

Key words: cabergoline, hyperprolactinemia, cardiac valvulopathy

1. Dept Endocrinology, St Bartholomew's Hospital, London EC1A 7BE, UK
2. JJR Macleod Centre for Diabetes, Endocrinology & Metabolism (Mac-DEM), Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB25 2ZP, UK
3. Institute of Metabolism and Systems Research, School of Clinical and Experimental Medicine, University of Birmingham, Wolfson Drive, Edgbaston, Birmingham B15 2TT, UK
4. Dept Endocrinology, The Christie NHS Foundation Trust, Wilmslow Road, Manchester, M20 4BX, UK
5. Neurosciences and Mental Health Research Institute, School of Medicine, Cardiff University, Cardiff, CF24 4HQ, UK
6. Diabetes and Endocrine Centre, Royal Bournemouth Hospital, Castle Lane East, Bournemouth, Dorset, BH7 7DW, UK
7. Dept Endocrinology, University College London Hospital, 235 Euston Road, London, NW1 2BU, UK
8. Queen's Hospital, Rom Valley Way, Romford, Essex, RM7 0AG, UK
9. Dept of Endocrinology, Leeds Centre for Diabetes & Endocrinology, St James's University Hospital, Leeds, LS9 7TF, UK
10. Department of Endocrinology, Queen Elizabeth Hospital, University Hospitals Birmingham, NHSFT, Edgbaston, Birmingham, B15 2TH, UK
11. Imperial Centre for Endocrinology, Imperial College Healthcare NHS Trust, London. W6 8RF, UK
12. Department of Endocrinology, Royal Devon & Exeter Hospital, University of Exeter Medical School, Exeter, EX2 4TP, UK
13. Institute of Cardiovascular Research, Royal Holloway, University of London (ICR2UL) & Ashford and St Peter's NHS Foundation Trust, Surrey, TW20 0EX, UK.
14. Dept Cardiology, University Hospitals Birmingham NHS Foundation Trust, Birmingham B15 2TH, UK

### **Address for correspondence:**

Prof WM Drake, Dept Endocrinology, St Bartholomew's Hospital, London EC1A 7BE, UK

Tel: +44 203 465 7264. Fax: +44 203 465 6148. Email: w.m.drake@qmul.ac.uk

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<sup>1,2,2,3</sup>, 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 drug<sup>4</sup>.

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<sup>5-7,7-15</sup>. 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 DAs<sup>16</sup>. 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 compared<sup>16</sup>. 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 ( $\leq 10$  mm) or  
63 macroadenoma ( $\geq 10$  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 echocardiogram<sup>17</sup>. 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)<sup>18</sup>. 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<sup>4,19</sup>. 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<sub>2B</sub>) 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 dysfunction<sup>20</sup>. 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 months<sup>1</sup>,  
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 1/20<sup>th</sup> – 1/40<sup>th</sup> 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 Kingdom<sup>19</sup> at a time when both public and private healthcare providers are seeking to  
151 ensure use of cardiovascular imaging is appropriate<sup>21</sup>. 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's<sup>1</sup> came more than two  
155 decades after the first clinical trials of DA agonist use in hyperprolactinemia<sup>22</sup>. 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<sup>5,7,8</sup>

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<sup>7,23</sup>. Moreover, while grading the extent of valve  
175 calcification is an important factor in predicting outcome in AS<sup>24</sup>, visual estimation on 2D

176 echocardiography is subjective and has high inter-observer variability<sup>25</sup>. 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 half<sup>26</sup>. 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 technicians<sup>27</sup>.  
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 hospitals<sup>28</sup>. 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 regurgitation<sup>29</sup>.

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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