GUIDELINES AND RECOMMENDATIONS

Echocardiography and monitoring patients receiving dopamine agonist therapy for hyperprolactinaemia: a joint position statement of the British Society of Echocardiography, the British Heart Valve Society and the Society for Endocrinology

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*(V Sharma is the Guidelines Chair)

Abstract

This is a joint position statement of the British Society of Echocardiography, the British Heart Valve Society and the Society for Endocrinology on the role of echocardiography in monitoring patients receiving dopamine agonist (DA) therapy for hyperprolactinaemia. (1) Evidence that DA pharmacotherapy causes abnormal valve morphology and dysfunction at doses used in the management of hyperprolactinaemia is extremely limited. Evidence of clinically significant valve pathology is absent, except for isolated case reports around which questions remain. (2) Attributing change in degree of valvular regurgitation, especially in mild and moderate tricuspid regurgitation, to adverse effects of DA in hyperprolactinaemia should be avoided if there are no associated pathological changes in leaflet thickness, restriction or retraction. It must be noted that even where morphological change in leaflet structure and function may be suspected, grading is semi-quantitative on echocardiography and may vary between different machines, ultrasound settings and operators. (3) Decisions regarding discontinuation of medication should only be made after review of serial imaging by an echocardiographer experienced in analysing drug-induced valvulopathy or carcinoid heart disease. (4) A standard transthoracic echocardiogram should be performed before a patient starts DA therapy for hyperprolactinaemia. Repeat transthoracic echocardiography should then be performed at 5 years after starting cabergoline in patients taking a total weekly dose less than or equal to 2 mg. If there has been no change on the 5-year scan, repeat echocardiography could continue at 5-yearly intervals. If a patient is taking more than a total weekly dose of 2 mg, then annual echocardiography is recommended.

Key Words
- dopamine agonist
- transthoracic echocardiography
- hyperprolactinaemia
- monitoring
- valve disease

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Introduction

It is more than ten years since the publication of a large population-based nested case-control study (1) and an echocardiographic prevalence study (2) reporting an association between the use of pergolide and cabergoline for the treatment of symptomatic Parkinson’s disease (PD) and an increased risk of restrictive valvular heart disease. These and other studies (3) led to the voluntary withdrawal of pergolide from the US market in 2007. While pergolide was used predominantly in PD, cabergoline is used more commonly in the treatment of hyperprolactinaemia. Dopamine agonists (DA) are first-line therapy for the treatment of hyperprolactinaemia because of excellent biochemical and tumoural control in the majority of patients, the alternative being surgery with or without radiotherapy, exposing patients to the risks of hypopituitarism (4). Cabergoline is generally the agent of choice because alternatives, such as bromocriptine, require multiple daily doses and have a less favourable side effect profile. The use of cabergoline in PD and hyperprolactinaemia differs considerably. Cabergoline is used in PD patients over a shorter period (months) at much higher dose (typically 3 mg a day) compared to a much longer period of treatment (years) at lower doses (typically 0.5–1 mg weekly) in hyperprolactinaemic patients (5). Moreover, while there are a number of effective alternative drugs in the treatment of PD, medical options for the treatment of hyperprolactinaemia are more limited. As a result of the studies documenting an increased risk of valvulopathy in PD patients, the Medicines and Healthcare products Regulatory Agency (MHRA) recommended that physicians in the United Kingdom should request baseline echocardiography to exclude valvular heart disease in all patients before starting cabergoline or bromocriptine, followed by a second echocardiogram performed 3–6 months after commencement and then at 6–12-month intervals while continuing on the medication. It was also recommended that treatment be stopped if echocardiography showed worsening or new valvular restriction, thickening or regurgitation. In the intervening years, much echocardiographic data from cabergoline-treated hyperprolactinaemic patients has been published. Most of these data suggest that the risk of developing significant valvular heart disease is negligible and not a cause for clinical concern. Despite this, constraints imposed by the working relationship between the MHRA and the EMA dictate that the published recommendations are unlikely to be revised. This position statement, endorsed by the British Society of Echocardiography, the British Heart Valve Society and the Society for Endocrinology has been written to provide endocrine and cardiac physicians with practical guidance in this area based on a contemporary review of the available literature.

Pathophysiology

The possibility that cabergoline might cause cardiac valvulopathy is pharmacologically and mechanistically plausible. Like other ergot-based drugs (e.g. methysergide and the weight loss drugs fenfluramine and dexfenfluramine), cabergoline binds to the serotonin receptor subtype 2B (5-HT$_{2B}$) located on heart valves. Activation of these receptors induces valvular interstitial cell mitogenesis and proliferation, which in turn modifies the quantity and quality of the valvular extracellular matrix through actions on proteoglycans, collagen types I, III and IV, and matrix metalloproteinases (6). As a result, valve leaflets and chords become thickened, retracted and stiff, leading most commonly to valvar regurgitation (Videos 1 and 2). The histopathological appearance of valves affected by DA agonists is akin to that caused by carcinoid syndrome, with deposition of plaque-like material consisting of myofibroblasts within a fibromyxoid stroma (7). An association was found between higher cumulative doses of pergolide and cabergoline and the severity of cardiac valvular regurgitation in PD patients and, in particular, with the mitral valve tenting area, a subclinical index of leaflet stiffening and thickening (3). This quantitative method for measuring the impact of DA on valve function is important for the interpretation of the prolactinoma literature for a number of reasons. First, without careful blinding, there is evidence that subjective assessment tends to result in overestimation of valvulopathy (8). Secondly, most studies report only the degree of valve regurgitation and any assessment of leaflet thickening and retraction is subjective. Thirdly machine settings are not standardized, particularly the use of fundamental instead of second harmonic imaging. Harmonic imaging is a technique that employs the resonance characteristics of tissue to produce images with higher resolution and fewer artefacts than conventional (fundamental) imaging. Harmonic imaging is the principal technique now used in echocardiography, but overestimates leaflet thickness compared to fundamental imaging. Finally, most studies within the prolactinoma literature only reported on the prevalence of any valvular lesion as
detected by echocardiography, without distinguishing cabergoline-associated valvulopathy from coincidental abnormalities that may often be found in patients in the United Kingdom of similar age to those studied (9).

**Video 1**

Tilted parasternal long axis view of the tricuspid valve demonstrating thickening, retraction and fixation of the leaflets. View Video 1 at [http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0069/video-1](http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0069/video-1).

**Video 2**

Colour flow Doppler demonstrating severe tricuspid regurgitation. View Video 2 at [http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0069/video-2](http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0069/video-2).

**Current evidence**

Following publication of the adverse effects of DA agonists at high dose in PD, several groups published single institution, cross-sectional case-control studies investigating the link between chronic DA therapy at low dose in hyperprolactinaemia and the presence of valvular abnormalities (10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23) (Table 1). These were all limited by small size. Moreover, the control groups in each study contained only healthy individuals or those referred for other cardiac symptoms, for example palpitations, who were then found to have normal echocardiography, rather than untreated patients with hyperprolactinaemia. One study in 50 patients found an increase in the prevalence of moderate (27/50; 54%) but not of mild tricuspid regurgitation (TR) among those treated with cabergoline at a median dose 280 mg for a median duration of 72 months compared to controls (9/50; 18%) (11). The distinction between mild and moderate TR was made in this article by the extent to which retrograde flow filled the atrium, which is a method known to be subject to error, and technical and haemodynamic variation. Furthermore, the difference in degree of TR was found in the absence of any changes to the thickness or restriction of the valve leaflets. In another study of 78 patients (mean cumulative dose 363 mg; mean treatment duration 60 months), mild TR was found more often (32/78, 41%) among those taking DA agonists than in controls (20/78, 26%), although there was no graded association with cumulative dose and there was no difference in ‘clinically significant’ valve disease (12). Again, the difference in degree of TR was found in the absence of any changes to the thickness or restriction of the valve leaflets. The same study also suggested an increase in aortic calcification, which is difficult to understand from a pathophysiological perspective and has not been replicated elsewhere. Thereafter, two more similar-sized case-controlled studies suggested other morphological changes (13, 17). In 102 patients (mean cumulative cabergoline dose 204 mg; mean treatment duration 79 months) (13), there was an increase in mitral valve tenting area but no difference in leaflet thickness and no change in any other valves. In 103 patients (mean cumulative cabergoline dose 174 mg; mean treatment duration 46 months) (17), there was a new category of ‘sub-clinical fibrosis’, defined by increased leaflet echogenicity and/or increased cusp thickness (>3 mm mitral; >2 mm other valves) but with no difference in the degree of regurgitation. These data also contrast with the results of ten similar-sized, single institution case-control studies that found no link between DA use and significant restrictive valve defects or regurgitation (10, 14, 15, 16, 18, 19, 20, 21, 22, 23). Finally, a large multi-centre cross-sectional study based in the United Kingdom of 747 patients taking DA agonists (median cabergoline dose 152 mg) showed no association between cumulative doses of cabergoline or bromocriptine and the age-corrected prevalence of valvular abnormalities (24). In summary, case-control studies investigating DA agonist valvulopathy in hyperprolactinaemia have provided poor quality data, using different diagnostic criteria, multiple testing in small groups and lack of standardized assessment of valve morphology. There are isolated case reports of restrictive valve disease after cabergoline but these have either been in cases treated with high dose (8, 25) or in patients with co-morbidity (26), and in one case developing bowel obstruction after diagnosis of DA valvulopathy without exclusion of coexisting neuroendocrine tumour (27).

In addition to the cross-sectional, case-control studies, there have been three studies with serial follow-up (Table 2). The first, small, single-centre study examined 45 patients receiving cabergoline for prolactinoma (mean cabergoline dose 401 mg) with baseline and then repeat echocardiography at 2 years, and found neither valve stenosis nor development of valvular regurgitation (28). In a follow-up of 192/747 patients from the original cross-sectional study by Drake et al., with median duration of cabergoline therapy 34 (24–42) months, no association was found between cumulative doses of cabergoline and clinically significant valvular abnormality (5). The third study followed 100 subjects for a median interval
62.5 (34.8–77) months between echocardiography following a median total duration of cabergoline therapy for 124.5 months (median dose 277.8 mg) and found no significant alterations in valve structure or function (29). One of these studies had a median follow-up of 10 years, although the potential expected duration of treatment with cabergoline can sometimes be longer.

Meta-analyses have been performed however, that suggest a small effect may be present, although again there are limitations to these statistical studies (30, 31, 32). First, the meta-analyses have all been influenced by data from one early single-centre case-control study, in which 27/50 (54%) patients compared to 9/50 (18%) controls were reported as having moderate to severe TR (11). Interestingly, the same group subsequently reported a follow-up study in which there were no reported differences in the risk of TR between controls and cabergoline-treated patients. Secondly, although these meta-analyses indicated a possible increased risk of mild to moderate TR, they were not associated with the typical features of valve thickening and restriction, and no clinically significant valve lesions were identified. If, as is widely accepted, it is the interaction of cabergoline with 5HT2B receptors that mediates the abnormal valvular function then, by analogy with carcinoid heart disease, this should be accompanied by characteristic changes in valve morphology (leaflet thickening, restricted movement and calcification). A major barrier to progress in the field is the fact that long-term, detailed studies of the size sufficient to exclude an effect would be costly to perform and require considerable expertise to ensure consistent, reliable and quantitative echocardiographic

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**Table 1** Case-control studies and results.

| Study, year               | Cases (male%) | Controls (male%) | Age cases ± S.D. | Cumulative dose (mg) ± S.D. | Duration Rx (months) ± S.D. | Summary                                                                 |
|--------------------------|--------------|------------------|------------------|-----------------------------|-----------------------------|------------------------------------------------------------------------|
| Bogazzi 2008 (10)        | 100 (21)     | 100 (16)         | 41 ± 13          | 279 ± 301                   | 67 ± 39                    | No effect                                                              |
| Boguszewski 2012 (21)    | 51 (27)      | 59 (27)          | 42.3 ± 13.5      | 239 ± 243                   | 38 ± 21                    | ↑ MV tenting; ↑ mild TR (7.8% vs 0%); ↑ mild PR (no statistics presented) |
|                          |              |                  |                  |                             |                             | ↑ mod TR (54% vs 18%); No other difference in VD                      |
| Colao 2008 (11)          | 50 (12)      | 50 (12)          | 36.5 ± 10.5      | 414 ± 390                   | 81 ± 37                    | No effect                                                              |
| Cordoba-Soriano 2013 (23)| 8 (25)       | 11 (34)          | 38.8 ± 10.4      | 158 (median)                | 46                         | ↑ subclinical fibrosis (40% vs 23%); No other difference in VD         |
| Elenkova 2012 (17)       | 103 (20)     | 102 (21)         | 38.6 ± 9.93      | 174 (no SD)                 | 47 ± 286                   | No effect                                                              |
| Halperin 2012 (40)       | 15 (40)      | 58 (10)          | No data          | 523 (median)                | No data                    | ↑ mild TR (41% vs 26%); ↑ AV calcification                            |
| Herring 2009 (18)        | 50 (60)      | 50 (60)          | 51.2 ± 15.5      | 443 ± 375                   | 79 ± 42                    | ↑ MV tenting; No other difference in VD                                |
| Kars 2008 (12)           | 47 (28)      | 78 (26)          | 46 ± 13          | 363 ± 377                   | 62 ± 32                    | ↑ mild TR (41% vs 26%); ↑ AV calcification                            |
| Lancellotti 2008 (13)    | 102 (28)     | 51 (37)          | 51 (median)      | 184 ± 105                   | 79 (median)                | No effect                                                              |
| Nachtigall 2010 (20)     | 100 (48)     | 100 (48)         | 44 ± 13          | 253 ± 520                   | 48 ± 40                    | ↑ subclinical fibrosis (40% vs 23%); No other difference in VD         |
| Tan 2010 (15)            | 72 (26)      | 72 (28)          | 36 (median)      | 126 (median)                | 53 (median)                | No effect                                                              |
| Vallette 2009 (16)       | 70 (47)      | 70 (47)          | 44 ± 13          | 282 ± 271                   | 55 ± 22                    | ↑ OR mild TR; mild PR; No other difference in VD                       |
| Wakil 2008 (14)          | 44 (27)      | 566 (32)         | 41.8 ± 13.2      | 279 ± 301                   | 44.8                       | No effect                                                              |

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**Table 2** Serial follow-up studies and results.

| Study, year, year         | Gender (male%) | Age at first echo ± S.D. | Cumulative dose at first echo (mg) ± S.D. | Cumulative dose at second echo (mg) ± S.D. | Duration Rx at first echo (months) ± S.D. | Duration Rx at second echo (months) ± S.D. | Summary                                                                 |
|---------------------------|----------------|--------------------------|-------------------------------------------|-------------------------------------------|-------------------------------------------|-------------------------------------------|------------------------------------------------------------------------|
| Auriemma 2013 (41)        | 11 (28)        | 38.7 ± 12.5              | No data                                   | 149 (median)                             | No data                                   | 60 ± 0                                    | No effect                                                              |
| Delgado 2012 (28)         | 13 (29)        | 48 ± 12.1                | 355 ± 369                                 | 401 ± 369                                | 62.4 ± 32.4                               | 86.4 ± 32.4                               | ↑ AV calcification (63% vs 38%); No effect                             |
| Vroonen 2017 (29)         | 30 (30)        | No data                  | 139.4 (median)                            | 278 (median)                             | 62.5 (median)                             | 124.5 (median)                            | No effect                                                              |
assessment. It is important to note that in all studies performed, bromocriptine has not been implicated with any valvular abnormalities.

Alternative imaging modalities, for example cardiovascular magnetic resonance imaging, do not provide adequate spatial or temporal resolution to compete with echocardiography for detailed assessment of valve structure and function. Moreover, a prospective, placebo-controlled design among young women with hyperprolactinaemia and oligo-amenorrhoea would be unethical, and any effects of cabergoline would be impossible to separate from those caused by/associated with restoration of physiological oestrogen secretion. The expectation that existing clinical networks could produce accurate, large volume data by applying current MHRA guidelines on surveillance by echocardiography also appears unlikely, since adherence to current recommendations is poor. In a service evaluation performed by NHS Highland (North), only 2/45 patients started on a DA agonist had echocardiography prior to starting therapy (33).

**Recommendations on surveillance**

Echocardiography is accepted as the gold standard technique for assessment of native valve structure and function (34). The detection of changes in structure and function in native valves may be subtle and echocardiography should be performed by properly trained, accredited professionals (35). In each case, a standard transthoracic study should be performed following minimum standards (36). In addition to this, however, careful attention should be taken to perform semi-quantitative assessment of valve structure and function to detect the changes typical of DA agonist therapy. Although there are no methods validated for assessment in DA agonist therapy per se, the changes to be detected are the same as those in patients with carcinoid heart disease, for which there are validated scoring systems with high feasibility and discriminatory value (37). Of these, the most sensitive and specific is an echocardiographic scoring system that assesses leaflet thickening, mobility and morphology, severity of valvular regurgitation and stenosis, and the haemodynamic effects on (right) ventricular size and function with good inter-observer agreement (38). Moreover, this incorporates assessment of all four cardiac valves, although focusses on haemodynamically significant right-sided valvular lesions through secondary effects on right ventricular size and function, which have been most frequently identified in the literature in DA agonist therapy (Table 3). Although tenting area has been used to quantify stiffening, this has not been validated in large studies and repeatability and reproducibility are not known, so that this is not a recommended feature for screening and follow-up.

Given that one of the major difficulties with the existing literature is the separation of valve disease due to DA agonist therapy from pre-existing changes in valve structure and function, it is recommended that all patients starting DA agonist therapy should undergo a transthoracic echocardiogram before drug therapy is commenced (Table 4). An increase in valve score may then be interpreted in the clinical context, considering the age and sex of the patient, the impact of other factors on valve leaflet thickening, mobility and morphology (e.g. ageing, chronic kidney disease), and likely impact of DA agonist (total dosage and exposure). The main problem in clinical practice will be the use of such a score in patients who were on a DA agonist for some time and in whom there may be changes identified on echocardiography. There have been no prospective validation studies of a scoring system and therefore, it is not possible to give a value or ‘score’ above which a patient should be categorized as affected by DA valvopathy. The sensitivity of the scoring system for identifying changes in patients with carcinoid increases with increasing score, with a median score in those affected 12 (range 8–21) and in those not affected 2 (IQR 1–3) (37). It could be argued that routinely
Table 4 Summary of recommendations for patients receiving dopamine agonist therapy in hyperprolactinaemia.

| Recommendations                                                                 |
|---------------------------------------------------------------------------------|
| 1. All patients should undergo echocardiography before commencing DA therapy.   |
| 2. Patients taking a dose of cabergoline of ≤2 mg/week should undergo surveillance echocardiography at 5 years. |
| 3. Patients taking a dose of cabergoline of >2 mg/week should undergo annual echocardiography. |
| 4. Patients taking a dose of ≤2 mg/week who develop a change in valve function should undergo annual echocardiography if treatment is to continue. |
| 5. Decisions regarding discontinuation of medication should only be made after review of serial imaging by an echocardiographer experienced in analysing drug-induced valvulopathy or carcinoid heart disease. |

Conclusions

Evidence that DAs cause valvulopathy akin to carcinoid heart disease in patients with hyperprolactinaemia is limited to a very small number of isolated case reports in which the cumulative doses used were very high and not dissimilar to those reported in the original studies on PD patients. The finding of valvular regurgitation in a patient taking cabergoline for hyperprolactinaemia does not, in the absence of typical valvular structural changes, mandate discontinuation of the drug. Any decision about discontinuation of the drug should be a multidisciplinary one, in discussion with the patient, and consideration should be given to the replacement with bromocriptine. Ongoing collection of high-quality data, via collaborative audit and study initiatives, together with post-marketing reporting (e.g. ‘yellow card’ reports in the United Kingdom) of independently confirmed cases, is strongly encouraged.

Declaration of interest

Vishal Sharma is Co-Editor-in-Chief, Richard Steeds and John Chambers are strategic editors, and Guy Lloyd is an associate editor of Echo Research and Practice. They were not involved in the review or editorial process for this article, on which they are listed as an author. The other authors have nothing to disclose.

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Author contribution statement

R P S and W D conceived the work and wrote the text, C S collaborated and contributed for the text and the manuscript was reviewed and conclusions drawn with V S, G L and J C.
References

1. Schade R, Andersohn F, Sissa S, Haverkamp W & Garbe E. Dopamine agonists and the risk of cardiac-valve regurgitation. New England Journal of Medicine 2007 356 29–38. (https://doi.org/10.1056/NEJMoa062222)

2. Zanettini R, Antonini A, Gatto G, Gentile R, Tesi S & Pezzoli G. Valvular heart disease and the use of dopamine agonists for Parkinson’s disease. New England Journal of Medicine 2007 356 39–46. (https://doi.org/10.1056/NEJMoa064830)

3. Casanueva FF, Molitch ME, Schlechte JA, Abs R, Bonert V, Van Camp G, Flamez A, Cosyns B, Weytjens C, Muyldermans L, Zanettini R, Antonini A, Gatto G, Gentile R, Tesei S & Pezzoli G. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clinical Endocrinology 2006 65 265–273. (https://doi.org/10.1111/j.1365-2265.2006.02562.x)

4. Drake WM, Stiles CE, Bevan JS, Karavitaki N, Trainer PJ, Rees DA, Richardson TJ, Balfe CM, Stojanovic N, Murray RD, et al. A follow-up study of the prevalence of valvular heart abnormalities in hyperprolactinaemic patients treated with cabergoline. Journal of Clinical Endocrinology and Metabolism 2016 101 4189–4194. (https://doi.org/10.1210/jc.2016-2224)

5. Elangbam CS. Drug-induced valvulopathy: an update. Toxilogic Pathology 2010 38 837–848. (https://doi.org/10.1177/0192623310378027)

6. Pinerio A, Marcos-Alberca P & Fortes J. Cabergoline-related severe restrictive mitral regurgitation. New England Journal of Medicine 2005 353 1976–1977. (https://doi.org/10.1056/NEJM200510313531822)

7. Gu H, Luck S, Carroll PV, Powrie J & Chambers J. Cardiac valve disease and low-dose dopamine agonist therapy: an artefact of reporting bias? Clinical Endocrinology 2011 74 608–610. (https://doi.org/10.1111/j.1365-2265.2010.03973.x)

8. d’Arcy JL, Coffey S, Loudon MA, Kennedy A, Pearson-Stuttard J, Birks J, Frangou E, Farmer AJ, Mant D, Wilson J, et al. Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE Population Cohort Study. European Heart Journal 2016 37 3515–3522. (https://doi.org/10.1093/eurheartj/ehw229)

9. Bogazzi F, Buralli S, Manetti L, Raffaelli V, Cigni T, Lombardi M, Borei F, Taddei S, Salveti A & Martino E. Treatment with low doses of cabergoline is not associated with increased prevalence of cardiac valve regurgitation in patients with hyperprolactinaemia. International Journal of Clinical Practice 2008 62 1864–1869. (https://doi.org/10.1111/j.1742-1241.2008.01779.x)

10. Colao A, Galderisi M, Di Sarro A, Pardo M, Gaccione M, D’Andrea M, Guerra E, Pivonello R, Lerro G & Lombardi G. Increased prevalence of tricuspid regurgitation in patients with prolactinomas chronically treated with cabergoline. Journal of Clinical Endocrinology and Metabolism 2008 93 3777–3784. (https://doi.org/10.1210/jc.2007-1403)

11. Kars M, Delgado V, Holman ER, Feelders RA, Smit JW, Romaijn JA, Bax JJ & Pereira AM. Aortic valve calcification and mild tricuspid regurgitation but no clinical heart disease after 8 years of dopamine agonist therapy for prolactinoma. Journal of Clinical Endocrinology and Metabolism 2008 93 3348–3356. (https://doi.org/10.1210/jc.2007-2658)

12. Lancellotti P, Livadariu E, Markov M, Daly AF, Burlacu MC, Betea D, Pierard I & Beckers AM. Cardiobase and the risk of valvular lesions in endocrine disease. European Journal of Endocrinology 2008 159 1–5. (https://doi.org/10.1530/EJE-08-0213)

13. Wakil A, Rigby AS, Clark AL, Kaklivaikka-Bennett A & Atkin SL. Low dose cabergoline for hyperprolactinaemia is not associated with clinically significant valvar heart disease. European Journal of Endocrinology 2008 159 R11–R14. (https://doi.org/10.1530/EJE-08-0365)

14. Tan T, Cabrita IZ, Hensman D, Grogono J, Dhillo WS, Baynes KC, Eliaho J, Meenan K, Robinson S, Nihoyannopoulos P, et al. Assessment of cardiac valve dysfunction in patients receiving cabergoline treatment for hyperprolactinaemia. Clinical Endocrinology 2010 73 369–374. (https://doi.org/10.1111/j.1365-2265.2010.03827.x)

15. Vallette S, Serri K, Rivera J, Santagata P, Delorme S, Garfield N, Kahtani N, Beuregard H, Aris-Jilwan N, Houdé G, et al. Long-term cabergoline therapy is not associated with valvular heart disease in patients with prolactinomas. Pituitary 2009 12 153–157. (https://doi.org/10.1007/s11102-008-0134-2)

16. Elkenova A, Shabani R, Kalinov K & Zacharieva S. Increased prevalence of subclinical cardiac valve fibrosis in patients with prolactinomas on long-term bromocriptine and cabergoline treatment. European Journal of Endocrinology 2012 167 17–25. (https://doi.org/10.1530/EJ-12-0121)

17. Herring N, Szmitiegelski C, Becher H, Karavitaki N & Wass JAH. Valvular heart disease and the use of cabergoline for the treatment of prolactinoma. Clinical Endocrinology 2009 70 104–108. (https://doi.org/10.1111/j.1365-2265.2008.03488.x)

18. Lafeber M, Stades AM, Valk GD, Cramer MJ, Teding van Berkhout F, Senten W, van Zandijcke M, De Sutter J, Santens P, Decoodt P, Moerman C, et al. A case of iatrogenic severe mitral regurgitation. Monaldi Archives for Chest Disease 2010 75 28. (https://doi.org/10.4081/ma-ch.2010.75)

19. Boguszewski CL, dos Santos CMC, Sakamoto KS, Marini LC, de Souza AM & Azevedo M. A comparison of cabergoline and bromocriptine on the risk of valvular heart disease in patients with prolactinomas. Journal of Endocrinology 2010 162 667–675. (https://doi.org/10.1530/EJE-09-0989)

20. Nachtigall LB, Valassi E, Jones L, McCarty D, Passet J, Biller BM, Miller KK, Utz A, Grinspoon S, Lawson EA, et al. Gender effects on cardiac valve function in hyperprolactinaemic patients receiving cabergoline: a retrospective study. Clinical Endocrinology 2010 72 52–58. (https://doi.org/10.1111/j.1365-2265.2009.03608.x)

21. Dojan BA, Arcdu A, Tuna MM, Berker D, Demirci N, Demirtas Ş, Çiçekcioğlu H & Güler S. Autoimmune fibrotic adverse reactions in hyperprolactinemic patients treated with cabergoline. Revista Española de Cardiología 2013 66 410–412. (https://doi.org/10.1016/j.recesp.2012.10.016)

22. Drake WM, Stiles CE, Howlett TA, Toogood AA, Bevan JS & Steeds RP. A cross-sectional study of the prevalence of cardiac valvular abnormalities in hyperprolactinemic patients treated with ergot-derived dopamine agonists. Journal of Clinical Endocrinology and Metabolism 2014 99 90–96. (https://doi.org/10.1210/jc.2013-2254)

23. Lafeber M, Stades AM, Valk GD, Cramer MJ, Teding van Berkhout F, Senten W, van Zandijcke M, De Sutter J, Santens P, Decoodt P, Moerman C, et al. A case of iatrogenic severe mitral regurgitation. Monaldi Archives for Chest Disease 2013 80 133–136. (https://doi.org/10.4081/monaldi.2013.75)

24. Izgi C, Feray H, Cevik C, Saltan Y, Mansuroglu D & Nugent K. Severe tricuspid regurgitation in a patient receiving low-dose cabergoline for the treatment of acromegaly. Journal of Heart Valve Disease 2010 19 797–800.

25. Cavood TJ, Bridgepan M, Hunter L & Cole D. Low-dose cabergoline causing valvar heart disease in a patient treated for prolactinoma. Internal Medicine Journal 2009 39 266–267. (https://doi.org/10.1111/j.1445-5994.2009.01920.x)

26. Delgado V, Biermaas NR, van Thiel SW, Ewe SH, Marsan NA, Holman ER, Feelders RA, Smit JW, Bax JJ & Pereira AM. Changes in...
heart valve structure and function in patients treated with dopamine agonists for prolactinomas, a 2-year follow-up study. Clinical Endocrinology 2012 77 99–105. (https://doi.org/10.1111/j.1365-2265.2011.04326.x)

29 Vroonen L, Lancellotti P, Garcia MT, Dulgheru R, Rubio-Almanza M, Maiga I, Magne J, Petrossians P, Auriemma R, Daly AF, et al. Prospective, long-term study of the effect of cabergoline on valvular status in patients with prolactinoma and idiopathic hyperprolactinemia. Endocrine 2017 55 239–245. (https://doi.org/10.1007/s12020-016-1120-5)

30 De Vecchis R, Esposito C & Ariano C. Cabergoline use and risk of fibrosis and insufficiency of cardiac valves. Meta-analysis of observational studies. Herz 2013 38 868–880. (https://doi.org/10.1007/s00059-013-3816-0)

31 Bogazzi F, Manetti L, Raffaelli V, Lombardi M, Rossi G & Martino E. Cabergoline therapy and the risk of cardiac valve regurgitation in patients with hyperprolactinemia: a meta-analysis from clinical studies. Journal of Endocrinological Investigation 2008 31 1119–1123. (https://doi.org/10.1007/BF03345662)

32 Stiles CE, Tetteh-Wayoe ET, Bestwick J, Steeds RP & Drake WM. A meta-analysis of the incidence of cardiac valve disease in hyperprolactinemic patients treated with cabergoline. Journal of Clinical Endocrinology and Metabolism 2018 104 523–538. (https://doi.org/10.1210/jc.2018-01071)

33 Gamble D, Fairley R, Harvey R, Farman C, Cantley N & Leslie SJ. Screening for valve disease in patients with hyperprolactinaemia disorders prescribed cabergoline: a service evaluation and literature review. Therapeutic Advances in Drug Safety 2017 8 215–229. (https://doi.org/10.1177/2042096617703647)

34 Baumgartner H, Falk V, Bax J, De Bonis M, Hamm C, Holm PJ, Jung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. European Heart Journal 2017 38 2739–2791. (https://doi.org/10.1093/eurheartj/ehx391)

35 Monaghan M. Training in echocardiography. Heart 1994 71 (4 Supplement) 2–5. (https://doi.org/10.1136/hrt.71.4 Suppl.2)

36 Wharton G, Steeds R, Allen J, Phillips H, Jones R, Kanagala P, Lloyd G, Masani N, Mathew T, Oxborough D, et al. A minimum dataset for a standard adult transthoracic echocardiogram: a guideline protocol from the British Society of Echocardiography. Echo Research and Practice 2015 2 G9–G24. (https://doi.org/10.1530/ERP-14-0079)

37 Dobson R, Cuthbertson DJ, Jones J, Valle JW, Keevil B, Chadwick C, Poston GP & Burgess MI. Determination of the optimal echocardiographic scoring system to quantify carcinoid heart disease. Neuropeuroendocrinology 2014 99 85–93. (https://doi.org/10.1159/000360767)

38 Bhattacharyya S, Toumanakis C, Caplin ME & Davar J. Usefulness of N-terminal pro-brain natriuretic peptide as a biomarker of the presence of carcinoid heart disease. American Journal of Cardiology 2008 102 938–942. (https://doi.org/10.1016/j.amjcard.2008.05.047)

39 Caputo C, Prior D & Inner WJ. The need for annual echocardiography to detect cabergoline-associated valvulopathy in patients with prolactinoma: a systematic review and additional clinical data. Lancet Diabetes and Endocrinology 2015 3 906–913. (https://doi.org/10.1016/S2213-8587(14)70212-8)

40 Halperin I, Aller J, Varela C, Mora M, Abad A, Doltra A, Santos AE, Batista E, García-Pavía P, Sitges M, et al. No clinically significant valvular regurgitation in long-term cabergoline treatment for prolactinoma. Clinical Endocrinology 2012 77 275–280. (https://doi.org/10.1111/j.1365-2265.2012.04349.x.)

41 Auriemma RS, Pivonello R, Perone Y, Grasso LF, Ferreri L, Simeoli C, Iacuaniello D, Gasperi M & Colao A. Safety of long-term treatment with cabergoline on cardiac valve disease in patients with prolactinomas. European Journal of Endocrinology 2013 169 359–366. (https://doi.org/10.1530/eje-13-0231)

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