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GUIDELINES

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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Summary

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 valvar 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. Note must be taken 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.

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If a patient is taking more than a total weekly dose of 2 mg, then annual echocardiography is recommended.

1 | INTRODUCTION

It is more than 10 years since the publication of a large population-based nested case-control study¹ and an echocardiographic prevalence study² 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 studies³ 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 tumoral 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 (BSE), the British Heart Valve Society (BHVS) and the Society for Endocrinology (SfE) has been written to provide endocrine and cardiac physicians with practical guidance in this area based on a contemporary review of the available literature.

2 | PATHOPHYSIOLOGY

The possibility that cabergoline might cause cardiac valvulopathy is pharmacologically and mechanistically plausible. Like other ergot-based drugs (eg, 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

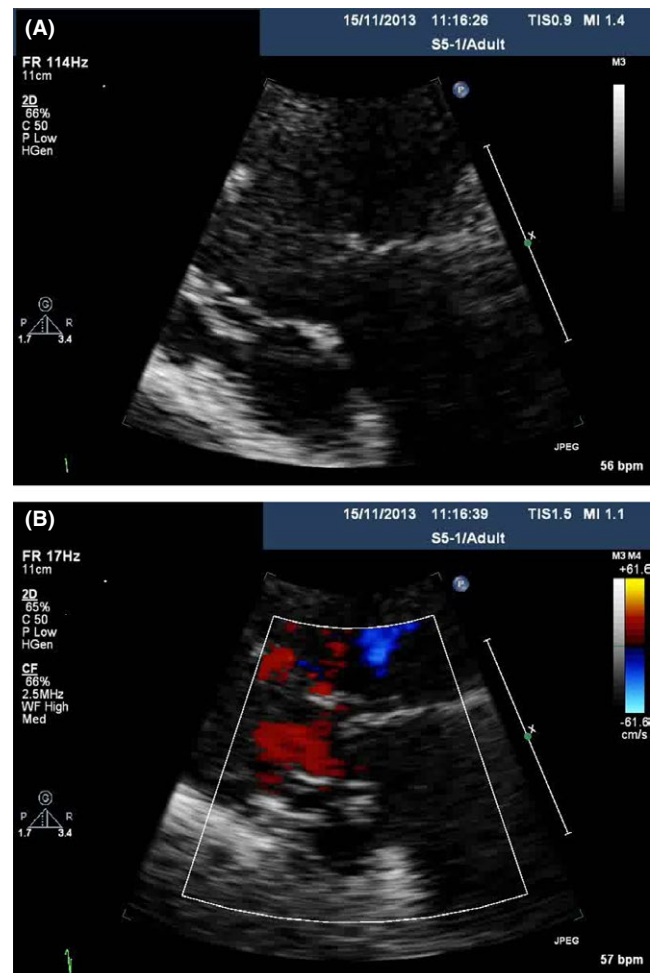


FIGURE 1 A, Tilted parasternal long axis view of the tricuspid valve demonstrating thickening, retraction and fixation of the leaflets. B, Colour flow Doppler demonstrating severe tricuspid regurgitation (Video format can be found in the Supporting Information)

TABLE 1 Case-control studies and results

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

Case-control studies in which patients were being treated for hyperprolactinemia with cabergoline for a minimum of 6 mo, a control group comparable to cases without history of DA therapy and had had an echocardiogram after ≥ 6 mo of cabergoline treatment. Values rounded to complete integer; mean \pm SD unless stated.

stiff, leading most commonly to valvular regurgitation (Figure 1A,B). 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. Firstly, without careful blinding, there is evidence that subjective assessment tends to result in over-estimation 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 over-estimates 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 UK of similar age to those studied.⁹

3 | 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 (Table 1).¹⁰⁻²³ 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, eg 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 paper 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 retraction of the valve leaflets. In another study of 78 patients (mean

TABLE 2 Serial follow-up studies and results

Study (y)	Gender (male %)	Age at first echo \pm SD	Cumulative dose At first echo (mg) \pm SD	Cumulative dose At second echo (mg) \pm SD	Duration Rx at first echo (mo) \pm SD	Duration Rx at second echo (mo) \pm SD	Summary
Auriemma (2013)	11 (28%)	38.7 \pm 12.5	No data	149 (median)	No data	60 \pm 0	No effect
Delgado (2012)	13 (29%)	48 \pm 12.1	355 \pm 369	401 \pm 369	62.4 \pm 32.4	86.4 \pm 32.4	\uparrow AV calcification (63% vs 38%)
Vroonen (2017)	30 (30%)	No data	139.4 (median)	278 (median)	62.5 (median)	124.5 (median)	No effect

cumulative dose 363 mg; mean treatment duration 60 months), mild tricuspid regurgitation 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 10 similar sized, single institution case-control studies that found no link between DA use and significant restrictive valve defects or regurgitation.^{10,14-16,18-23} 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 standardised 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 dopamine agonist valvulopathy without exclusion of co-existing 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} Firstly, 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-severe TR¹¹ 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-moderate tricuspid regurgitation, 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 5HT_{2B} 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 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 amongst young women with hyperprolactinaemia and oligo-amenorrhea 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

4 | 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 (eg, 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 have been

TABLE 3 Scoring system for patients receiving dopamine agonist therapy

	Normal = 0	Mild = 1	Moderate = 2	Severe = 3
Leaflet thickening	0	+	++	+++
Leaflet mobility	0	↓	↓↓	↓↓↓
Leaflet morphology	Normal	Stiff and straight	Mild retraction	Moderate-severe retraction
Stenosis	0	Mild	Moderate	Severe
Regurgitation	0	Mild	Moderate	Severe
RV dimension	0	>42 mm	RV = LV	RV forming the LV apex
RV function	0	↓	↓↓	↓↓↓

Adapted from Bhattacharya et al.³³

Recommendations

1. All patients should undergo echocardiography before commencing DA therapy
2. Patients taking a dose of cabergoline of ≤ 2 mg/weekly should undergo surveillance echocardiography at 5 y
3. Patients taking a dose of cabergoline of >2 mg/wk should undergo annual echocardiography
4. Patients taking a dose of ≤ 2 mg/wk 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

TABLE 4 Summary of recommendations for patients receiving dopamine agonist therapy in hyperprolactinaemia

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 performing a transthoracic echocardiogram before drug therapy is commenced may be unnecessary and that doing an echocardiogram if the dose is increased above 2 mg/wk may be sufficient. The approach in this guideline is conservative, since the existing case-control and longitudinal follow-up studies cannot definitively exclude a small effect in the longer term. Moreover, given the semi-quantitative nature of echocardiographic evaluation of the changes described in DA valvulopathy and the fact that some of these changes can be seen in other conditions, assessment before initiation of drug therapy is considered a pragmatic solution pending further data.

Given the worst-case scenario for potential progression based on the largest cohort with serial follow-up,⁵ it is recommended that repeat transthoracic echocardiography should be performed at 5 years after starting cabergoline in patients taking a total weekly dose ≤ 2 mg. If there has been no change on the 5-year scan, repeat echocardiography could continue at 5-yearly intervals. Within this time interval, there has been no evidence of major clinical change affecting patient outcome. There is an option for annual surveillance with auscultation, although there are no data regarding accuracy of this approach relative to the use of echocardiography.³⁹ If a patient is taking a total weekly dose of more than 2 mg, then annual echocardiography is recommended, although the number of these patients is small (see Table 4). Once cabergoline has been stopped, no further echocardiography is warranted assuming that no moderate or severe valve abnormality has been identified.

Given that grading is semi-quantitative, with subjective assessment of leaflet thickening, mobility and morphology, it is vital that follow-up studies are cross-checked by a different observer blinded to the initial echocardiographic score. Specifically, where there is a discrepancy >2 points in score, an echocardiographer with experience of patient monitoring for DA valvulopathy or with

experience in patients who have carcinoid heart disease should analyze the serial studies available in the patient before any decision is made regarding discontinuation of medication. It is critical to understand that changes in degree of regurgitation alone, for example from mild to moderate tricuspid regurgitation, should not on its own be sufficient to alter clinical management, especially without morphological change in leaflet motion, thickness or retraction.

5 | CONCLUSIONS

Evidence that dopamine agonists 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 of 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 multi-disciplinary one, in discussion with the patient, and consideration should be given to replacement with bromocriptine. Ongoing collection of high-quality data, via collaborative audit and study initiatives, together with post-marketing reporting (eg, "yellow card" reports in the UK) of independently confirmed cases, is strongly encouraged.

CONFLICT OF INTEREST

All authors have no conflict of interest that could be perceived as prejudicing the impartiality of the data reported.

AUTHOR CONTRIBUTIONS

RS and WD conceived the work and wrote the text, CS collaborated and contributed in this, and the manuscript was reviewed and conclusions drawn with GL and JC.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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