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

WM Drake[1], CE Stiles[1], JS Bevan[2], N Karavitaki[3], PJ Trainer[4], DA Rees[5], TI Richardson[6], SE Baldeweg[7], N Stojanovic[8], RD Murray[9], AA Toogood[10], NM Martin[11], B Vaidya[12], TS Han[13], RP Steeds[14], On behalf of the UK Cabergoline valvulopathy study group*, *FC Baldeweg[7], UE Sheikh[12], N Kyriakakis[9], S Parasuraman[2], L Taylor[14], N Butt[6], S Anyiam[4]

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 Dr, Edgbaston, Birmingham B15 2TT, UK; 4. Dept Endocrinology, The Christie NHS Foundation Trust, Wilmslow Rd, 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 Ln E, Bournemouth, Dorset, BH7 7DW, UK; 7. Dept Endocrinology, University College London Hospital, 235 Euston Rd, 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 Birmingha, 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

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

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

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

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

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Abbreviations:

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

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

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

Following the publication of a number of case reports, cohort studies and case-controlled series describing the association of short-term, intensive high dose cabergoline therapy for Parkinson's disease with cardiac valvulopathy (1, 2, 2, 3), guidance was issued by various medicines regulatory authorities recommending screening with transthoracic echocardiography (TTE) for all patients with hyperprolactinemic states on maintenance treatment with this class of drug (4).

Since then, a number of groups have contributed data to the literature in order to guide practice in this area. Most studies have reported TTE findings in modest numbers of patients with prolactinomas and compared them with healthy controls (5–7, 7–15). We have previously reported TTE data from a large (747 patients), multicenter, cross-sectional UK study of patients with hyperprolactinemia treated with DAs (16). Patients were divided into quartiles according to cumulative DA dose, with the lowest quartile acting as the 'reference group' against which higher quartiles of DA 'exposure' were compared (16). Here, longitudinal TTE findings are reported in a proportion of those patients, all of whom had received continuous DA therapy for at least 2 years in the intervening period.

Materials and Methods

Patients

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

Echocardiography

As in our previous study, all TTE examinations were performed by fully-trained sonographers in accordance with the British Society of Echocardiography minimum dataset for a standard adult transthoracic echocardiogram (17). Valve assessment included evaluation of morphology (leaflet thickening, calcification, mobility) and function of the mitral, aortic, pulmonary, and tricuspid valves in multiple views. Two-dimensional imaging was followed by color Doppler echocardiography after optimizing gain (to eliminate random speckle color from nonmoving regions) and Nyquist limit (50–60 cm/s) (18). Standard pulse wave and continuous wave Doppler examinations were performed. Valvular regurgitation was quantified as absent, mild, moderate, or severe by integrating multiple indices of severity (4, 19). As in our previous study, potentially clinically significant valvular disease (morphological or functional) was considered to be moderate or above.

Statistical Analysis

TTE parameters were described using medians and IQRs. The Wilcoxon signed rank test was used to compare parameters between the first and second studies. Generalized estimating equations, to take account of the repeated TTE measurements, were used to determine univariate odds ratios (ORs) for moderate or above abnormalities of any valve according to tertiles of cabergoline dose and patient characteristics. Generalized estimating equations with backwards selection were used to determine multivariate ORs. ORs were also calculated for mild or above valvular abnormalities. Statistical significance was taken as $P < .05$. All analyses were performed in Stata version 13 (StataCorp, College Station, Texas, USA).

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

Results

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

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

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

Discussion

In this study we have performed detailed, follow-up TTE in a large cohort of patients with hyperprolactinemia who, in addition to being exposed to DA therapy before the first examination, received uninterrupted treatment for at least two years before the second. Compared to our previous report, this cohort of patients contains a greater proportion of men and patients classified as having a macroad-

Table 1. Details of 9 moderate or above valvular lesions in 7 patients at the time of the second echocardiogram, together with details of cardiovascular (CV) risk factors, cumulative cabergoline (CAB) dose and other salient echocardiographic features to indicate the clinical significance of the valvular lesions observed. AR – aortic regurgitation; TR – tricuspid regurgitation; PR – pulmonary regurgitation; MR – mitral regurgitation; HTN – hypertension; ↑ Chol – hypercholesterolemia; IHD – ischaemic heart disease & LV/RV – left ventricle/right ventricle; Mod – moderate; LVED/Svol – left ventricular end-diastolic/systolic volume; IVS – interventricular septal dimension in diastole; PW – posterior wall thickness in diastole; RVID – right ventricular internal dimension in diastole; AV – aortic valve; TR V_{max} – maximum velocity of tricuspid regurgitation

Case	Gender	Age (yrs)	Echo 1	Echo 2	Cumulative CAB dose at 2nd echo (mg)	CV risk factors	Other echo features
1	Female	43	Mod TR	Mod TR	761.4	None	Normal RV size and function 1st and 2nd echo
2	Male	80	Mod AR	Mod AR	714.9	HTN	Normal LV size and function 1st and 2nd echo
						↑ Chol	LV IVS 1.4 cm PW 1.1 cm (1st echo)
						IHD	LV IVS 1.9 cm PW 1.3 cm (2nd echo)
3	Male	74	Mod TR; Mod MR; Mild PR	Mild TR; Mod MR; Mod PR	1192.1	HTN	Normal LV size and function 1st and 2nd echo
							Normal RV size and function 1st and 2nd echo
4	Male	92	Mod AR; Mod TR	Mod AR; Severe TR	354.6	IHD	Normal LV size and function 1st and 2nd echo
							Severe RV dilatation 2nd echo
							TR V_{max} 2.8 m/s 2nd echo
5	Male	80	Mild MR	Mod MR	2761.3	Smoker	LV dilatation 1st and 2nd echo
						HTN	LVEDvol 196mls; LVESvol 125 mls (1st echo)
						DM	LVEDvol 175 mls; LVESvol 140 mls (2nd echo)
						↑ Chol	Normal mitral valve leaflet morphology (1st echo)
						IHD	Diffuse mitral valve thickening (2nd echo)
6	Female	52	Mild TR	Mod TR	230.8	None	Normal LV size and function 1st and 2nd echo
							RVID base 3.5 cm (1st echo)
							RVID base 3.8 cm (2nd echo)
							TR V_{max} 2.1 m/s (1st echo)
							TR V_{max} 3.3 m/s (2nd echo)
7	Female	74	Mild MR	Mod MR	1059.8	IHD	Normal LV size and function 1st and 2nd echo
							Normal mitral valve leaflet morphology

Table 2. Odds ratio (OR) of any cardiac valvular abnormality (moderate or above and mild or above) by tertile of cumulative cabergoline exposure. In each set of ORs the lowest tertile of cabergoline exposure serves as the reference (ref) against which tertiles 2 and 3 are compared. *All ORs are age-adjusted.

	Any valvular abnormality moderate or above		Any valvular abnormality mild or above	
	OR* (95% CI)	p-value	OR (95% CI)	p-value
Cumulative cabergoline dose at first echocardiogram (mg)				
<35	1 (ref)		1 (ref)	
35–236	2.30 (0.51–10.31)	0.276	0.80 (0.45–1.42)	0.448
>236	3.09 (0.75–12.74)	0.118	0.88 (0.50–1.56)	0.663
Cumulative cabergoline dose at second echocardiogram (mg)				
<116	1 (ref)		1 (ref)	
116–405	1.07 (0.25–4.53)	0.931	0.55 (0.31–0.97)	0.040
>405	2.36 (0.66–8.49)	0.189	0.72 (0.40–1.29)	0.272
Cumulative cabergoline dose between echocardiograms (mg)				
<54	1 (ref)		1 (ref)	
54–123	2.57 (0.58–11.44)	0.214	0.73 (0.42–1.29)	0.284
>123	2.83 (0.63–12.74)	0.176	1.19 (0.67–2.12)	0.556
Months between echocardiograms				
<28.3	1 (ref)		1 (ref)	
28.3–40.5	2.15 (0.55–8.44)	0.274	1.62 (0.91–2.88)	0.102
>40.5	3.28 (0.85–12.64)	0.085	1.03 (0.59–1.82)	0.914

enoma. This is likely to reflect the higher background remission rate in women and of microadenomas such that some of these originally reported patients will have discontinued DA at some stage in the intervening period and not have been eligible for inclusion in this study. A patient population enriched with men and patients with macroadenomas is a useful one to study as it contains those most likely to need to continue DA therapy for a prolonged period of time. These data do not suggest a clinically significant effect of DA therapy at 'endocrine doses' on cardiac valvular function during medium-term follow-up and provide further reassurance to physicians using this class of drug for this clinical indication.

The background to the clinical question of the cardiac safety of DA has been extensively documented and summarized. Cabergoline binds to the same receptors (5-HT_{2B}) that mediate carcinoid heart disease, although there is no direct relationship between plasma levels of 5-HT and presence of valvulopathy suggesting that other factors may be required for the pathogenesis of valve dysfunction (20). Although cardiac valvulopathy may occur in patients with neurological disorders currently treated with doses of cabergoline up to 3 mg daily for more than 6 months (1), many endocrine physicians experienced in the management of pituitary disease were surprised by the various regulatory authority recommendations for TTE surveillance in patients with hyperprolactinemia. The doses involved in the treatment of hyperprolactinemia are, typically, approximately 1/20th – 1/40th of those used in the treatment of Parkinson's disease. Most lactotrope pituitary microadenomas occur in women, for whom either spontaneous remission or intervening pregnancies dictate that the drug is frequently prescribed for a limited period of time. Even if women require prolonged use of cabergoline for hyperprolactinemia, it is often possible to discontinue therapy at the time of the menopause. Our data suggest that the current recommendations (exclusion of cardiac valvulopathy before commencement of DA therapy; second TTE 3–6 months after starting treatment; and serial examinations at 6- to 12-month intervals while DA therapy is continued) are out of keeping with the risk of developing clinically significant valve disease. Based on estimates of the prevalence of lactotrope pituitary tumors, such a surveillance program would require an estimated 90 000 extra TTEs per year in the United Kingdom (19) at a time when both public and private healthcare providers are seeking to ensure use of cardiovascular imaging is appropriate (21). Nonfinancial implications, such as patient anxiety and inconvenience, are harder to quantify.

The publication of data regarding valvulopathy in patients with Parkinson's(1) came more than two decades after the first clinical trials of DA agonist use in hyperprolactinemia (22). There are major problems in designing studies to address the issue of possible cardiac valvulopa-

thy in patients taking 'endocrine doses'. Withholding DA therapy from patients with hyperprolactinemia (particularly women wanting to conceive) in order to perform controlled studies would clearly be unethical; and any postulated cardiac effects of DA therapy (positive or negative) would be hard to separate from any secondary changes that may occur as a consequence of normal gonadal steroid levels being restored to previously hypogonadal patients. Further, with the patent on cabergoline having died, large-scale multicenter phase IV studies in this area are improbable. Most of the literature in this area therefore comes from single-center studies of modest numbers of DA-treated patients compared to age-matched healthy controls. Most those studies have provided reassuring data regarding valve function, with just three reports of increased tricuspid regurgitation (moderate in one, mild in two others) and an inconsistent relationship to the cumulative dose of drug (5, 7, 8)

To our knowledge, this is the largest follow-up echocardiographic study of hyperprolactinemic patients treated with DA. Although the size is an obvious strength, as in our previous study, an obvious weakness is the lack of a true control group, with the lowest tertile of DA exposure serving as our 'surrogate control'. In an earlier follow-up study, statistically significant increases in aortic valve calcification were observed with DA therapy, although these changes did not translate into any alterations in valve function (7, 23). Moreover, while grading the extent of valve calcification is an important factor in predicting outcome in AS (24), visual estimation on 2D echocardiography is subjective and has high interobserver variability (25). This could simply be that cardiac valvulopathy develops over a prolonged time period and that clinically significant functional changes (defined in most studies as moderate severity or above) cannot be detected over the timescales of the reported studies. It was for this reason that we included an analysis based on 'mild or above severity' as a statistically significant increase in the prevalence of mild valvular abnormalities could provide preliminary evidence of developing clinically relevant valvulopathy. We found no evidence of an increase in mild anatomical or functional valvulopathy with increasing DA exposure.

Reassuring group data can sometimes conceal clinically important effects in small numbers of patients. It is for this reason that we present the details of the 9 moderate or above echocardiographic abnormalities in 7 patients seen at the second TTE; these cases illustrate some of the challenges of interpreting echocardiographic findings in this context. The median age of the 7 patients was 74; all except one patient was older than the median age of the overall cohort. Although this may suggest the observed abnormalities were age-related, this group of patients were also heavily exposed to DA; all except one patient had received a cumulative cabergoline dose above the median for the overall cohort. In case 5, for example, while the risk factor profile and documented history of IHD may well have been important factors in the progressive mitral regurgitation, the appearance of thickening of the valve leaflets is also compatible with DA therapy being etiologically contributory. Determining which echocardiographic abnormalities carry clinical significance is also difficult. Current echocardiography systems such as those used in this study detect 'physiological' tricuspid regurgitation in almost all subjects and 'physiological' mitral regurgitation in more than half (26). While 'trivial' and 'mild' regurgitation are so common, it is also recognized that significant reporter bias exists when information about the use of DA in patients undergoing surveillance TTE is provided to cardiac technicians (27). Moreover, quantification, even when using recognized methodology including vena contracta and proximal isovelocity surface area, is only modestly reliable; interobserver agreement for grading mitral regurgitation as severe or nonsevere is only 0.28 between specialists working in academic hospitals (28). In patients with less severe regurgitation, not only will interobserver variability be higher but there may well be physiological variation that will cause some change in categorisation. It is not clear whether newer imaging modalities such as cardiac magnetic resonance imaging (MRI) will provide more accurate or reproducible assessment of mild degrees of regurgitation (29).

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

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Address all correspondence and requests for reprints to: 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.

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References

1. **Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E.** Dopamine agonists and the risk of cardiac-valve regurgitation. *N Eng J Med*. 2007;356:29–38.
2. **Van CG, Flamez A, Cosyns B et al.** Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease. *Lancet*. 2004;363:1179–1183.
3. **Zanettini R, Antonini A, Gatto G, Gentile R, Tesei S, Pezzoli G.** Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Eng J Med*. 2007;356:39–46.
4. **MHRA.** Ergot-derived dopamine agonists:risk of fibrotic reactions in chronic endocrine uses. 2008.
5. **Colao A, Galderisi M, Di SA et al.** Increased prevalence of tricuspid regurgitation in patients with prolactinomas chronically treated with cabergoline. *J Clin Endocrinol Metab*. 2008;93:3777–3784.
6. **Bogazzi F, Buralli S, Manetti L et al.** Treatment with low doses of cabergoline is not associated with increased prevalence of cardiac valve regurgitation in patients with hyperprolactinaemia. *Int J Clin Pract*. 2008;62:1864–1869.
7. **Kars M, Delgado V, Holman ER et al.** Aortic valve calcification and mild tricuspid regurgitation but no clinical heart disease after 8 years of dopamine agonist therapy for prolactinoma. *J Clin Endocrinol Metab*. 2008;93:3348–3356.
8. **Wakil A, Rigby AS, Clark AL, Kallvikbacka-Bennett A, Atkin SL.** Low dose cabergoline for hyperprolactinaemia is not associated with clinically significant valvular heart disease. *Eur J Endocrinol*. 2008;159:R11–R14.
9. **Vallette S, Serri K, Rivera J et al.** Long-term cabergoline therapy is not associated with valvular heart disease in patients with prolactinomas. *Pituitary*. 2009;12:153–157.
10. **Tan T, Cabrita IZ, Hensman D et al.** Assessment of cardiac valve dysfunction in patients receiving cabergoline treatment for hyperprolactinaemia. *Clin Endocrinol (Oxf)*. 2010;73:369–374.
11. **Lancellotti P, Livadariu E, Markov M et al.** Cabergoline and the risk of valvular lesions in endocrine disease. *Eur J Endocrinol*. 2008; 159:1–5.
12. **Elenkova 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. *Eur J Endocrinol*. 2012;167:17–25.
13. **Herring N, Szmigielski C, Becher H, Karavitaki N, Wass JA.** Valvular heart disease and the use of cabergoline for the treatment of prolactinoma. *Clin Endocrinol (Oxf)*. 2009;70:104–108.
14. **Lafeber M, Stades AM, Valk GD, Cramer MJ, Teding van BF, Zelissen PM.** Absence of major fibrotic adverse events in hyperprolactinemic patients treated with cabergoline. *Eur J Endocrinol*. 2010;162:667–675.
15. **Nachtigall LB, Valassi E, Lo J et al.** Gender effects on cardiac valvular function in hyperprolactinaemic patients receiving cabergoline: a retrospective study. *Clin Endocrinol (Oxf)*. 2010;72:53–58.
16. **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. *J Clin Endocrinol Metab*. 2014;99:90–96.
17. **Wharton G, Steeds R, Allen J et al.** A minimum dataset for a standard adult transthoracic echocardiogram: a guideline protocol from the British Society of Echocardiography. *Echo Res Pract*. 2015;2:G9–G24.
18. **British Society of Echocardiography Education Committee. A minimum dataset for a standard transthoracic echocardiogram. 2016.**
19. **Sherlock M, Toogood AA, Steeds R.** Dopamine agonist therapy for hyperprolactinaemia and cardiac valve dysfunction; a lot done but much more to do. *Heart*. 2009;95:522–523.
20. **Bhattacharyya S, Jagroop A, Gujral DM et al.** Circulating plasma and platelet 5-hydroxytryptamine in carcinoid heart disease: a pilot study. *J Heart Valve Dis*. 2013;22:400–407.
21. **Douglas PS, Garcia MJ, Haines DE et al.** ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 Appropriate Use Criteria for Echocardiography. A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance Endorsed by the American College of Chest Physicians. *J Am Coll Cardiol*. 2011;57:1126–1166.
22. **Ferrari C, Barbieri C, Caldara R et al.** Long-lasting prolactin-lowering effect of cabergoline, a new dopamine agonist, in hyperprolactinemic patients. *J Clin Endocrinol Metab*. 1986;63:941–945.
23. **Delgado V, Biermasz NR, van Thiel SW et al.** Changes in heart valve structure and function in patients treated with dopamine agonists for prolactinomas, a 2-year follow-up study. *Clin Endocrinol (Oxf)*. 2012;77:99–105.
24. **Rosenhek R, Binder T, Porenta G et al.** Predictors of outcome in severe, asymptomatic aortic stenosis. *N Eng J Med*. 2000;343:611–617.
25. **Quader N, Wilansky S, Click RL, Katayama M, Chaliki HP.** Visual Estimation of the Severity of Aortic Stenosis and the Calcium Burden by 2-Dimensional Echocardiography: Is It Reliable? *J Ultrasound Med*. 2015;34:1711–1717.
26. **Okura H, Takada Y, Yamabe A et al.** Prevalence and correlates of physiological valvular regurgitation in healthy subjects. *Circ J*. 2011;75:2699–2704.
27. **Gu H, Luck S, Carroll PV, Powrie J, Chambers J.** Cardiac valve disease and low-dose dopamine agonist therapy: an artefact of reporting bias? *Clin Endocrinol (Oxf)*. 2011;74:608–610.
28. **Biner S, Rafique A, Rafii F et al.** Reproducibility of proximal isovelocity surface area, vena contracta, and regurgitant jet area for assessment of mitral regurgitation severity. *JACC Cardiovasc Imaging*. 2010;3:235–243.
29. **Gatehouse PD, Rolf MP, Graves MJ et al.** Flow measurement by cardiovascular magnetic resonance: a multi-centre multi-vendor study of background phase offset errors that can compromise the accuracy of derived regurgitant or shunt flow measurements. *J Cardiovasc Magn Reson*. 2010;12:5.