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Systematic Review and Meta Analysis

The effect of first intervention on cardiac parameters in patients with acromegaly: a systematic review

Kevin A. Huynh,[1,2,3] Jin Al-Gully,[1,2,4] José M. Montero-Cabezas,[4] Linda E. Scheffers,[5] Marco J.T. Verstegen,[3] Nienke R. Biermasz,[1,2] and Eva C. Coopmans[1,2,*]

[1]Division of Endocrinology, Department of Medicine, Leiden University Medical Center, 2333 ZA Leiden, The Netherlands
[2]Center for Endocrine Tumors Leiden (CETL), Center for Pituitary Care, Leiden University Medical Center, 2333 ZA Leiden, The Netherlands
[3]Department of Neurosurgery, Leiden University Medical Center, 2333 ZA Leiden, The Netherlands
[4]Department of Cardiology, Leiden University Medical Center, 2333 ZA Leiden, The Netherlands
[5]Department of Pediatric Cardiology, Erasmus Medical Center—Sophia Children's Hospital, 3015 GD Rotterdam, The Netherlands

*Corresponding author: Division of Endocrinology, Department of Medicine, Leiden University Medical Center, Albinusdreef 2, 2333 ZA, Leiden, The Netherlands. Email: coopmanse@maasstadziekenhuis.nl

Abstract

Objective: Cardiovascular disease in acromegaly patients remains a major cause of morbidity and all-cause mortality. This systematic review investigates the effect of the first growth hormone-lowering intervention on cardiac parameters.

Design: Systematic review.

Methods: Studies evaluating cardiac parameters following the first intervention in acromegaly published up to February, 25, 2022 were included in this systematic review. Risk of bias was assessed using a modified Newcastle–Ottawa Scale and Joanna Briggs Institute Critical Appraisal Checklist. Primary treatment modalities included (transsphenoidal) surgery and medical treatment with first-generation somatostatin receptor ligands. Cardiac outcome measures were divided into cardiac structure (left ventricular hypertrophy [LVH], [indexed] left ventricular mass [LVM/LVMi]) and cardiac function (left ventricular ejection fraction [LVEF] and E/A ratio).

Results: Twenty-six studies (17 cohort studies and 9 case reports) were included out of 2541 potential studies. The risk of bias analysis categorized, 24 studies as low risk and 2 studies as intermediate risk. Disease-associated changes in cardiac structure and function generally improved in most studies following primary treatment. Left ventricular mass/left ventricular mass index significantly decreased in 9/15 studies and the prevalence of LVH in 3/13 studies. Left ventricular ejection fraction significantly increased in 9/14 studies and the E/A ratio in 6/7 studies. Despite the limited number of studies, cardiac structure improved more in patients achieving biochemical remission than in those failing to achieve biochemical remission.

Conclusions: Acromegaly associated structural and functional myocardial changes improve with both medical and surgical treatment. Normalizing or even reducing growth hormone/insulin-like growth factor 1 levels may be key in the prevention of further progression of cardiac involvement in acromegaly and adverse cardiac outcomes.

Keywords: acromegaly, transsphenoidal surgery, somatostatin analogs, cardiomyopathy, left ventricular hypertrophy, cardiac function

Significance

To our knowledge, this is the first systematic review that summarizes and appraises current literature on the effect of initial treatment for acromegaly on cardiac parameters. This systematic review demonstrates that acromegaly associated impairments of cardiac structure and function already improve after the first growth hormone (GH)-lowering treatment, and highlights the importance of reducing GH/insulin-like growth factor 1 (IGF-I) load to prevent the progression of cardiovascular comorbidity. This review also highlights the need for future research on the effect of novel therapeutic modalities on cardiac involvement in acromegaly. Understanding the effect on cardiac parameters guides individual treatment decisions of acromegaly patients and paves the way for future research and guidelines for the management of cardiovascular comorbidities in acromegaly.

Introduction

Acromegaly is a rare endocrine disorder caused by a growth hormone (GH)-secreting pituitary adenoma in the majority of cases.[1] Growth hormone hypersecretion leads to overproduction of insulin-like growth factor 1 (IGF-I).[2] Prolonged exposure to excessive plasma levels of GH and IGF-I causes the exemplary image of acromegaly characterized by coarsening of facial features, acral overgrowth, and respiratory and cardiovascular dysfunction.[3,4]

Prolonged exposure to excess GH and IGF-I is associated with cardiac growth, increased myocardial contractility, and changes in the vascular system (eg, increased arterial

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wall stiffness, endothelial dysfunction, and smooth muscle cell growth).[5] Cardiac complications in acromegaly patients include cardiac hypertrophy, valvulopathy, and moderate arrhythmias, whereas congestive heart failure is more rare and only occurs after long-term exposure to high GH and IGF-I levels.[6-9] Structural and functional cardiac changes in acromegaly define acromegalic cardiomyopathy (ACM). The onset of ACM is postulated by Saccà et al. to consist of 3 distinct phases. In the early stage of ACM initial cardiac hypertrophy, an increased heart rate, and high systolic output can be observed, altogether configuring the hyperkinetic syndrome.[10,11] When ACM worsens, signs of diastolic dysfunction and insufficient systolic function on effort appear due to more prominent cardiac hypertrophy.[10,11] In end-stage untreated disease, cardiac abnormalities may include systolic dysfunction at rest and overt heart failure with signs of dilated cardiomyopathy.[10,11]

Historically, cardiac involvement in acromegaly was estimated to reduce life expectancy by 10 years, with a doubling of standardized mortality rates due to cardiovascular disease (60%).[1,2] More recently, mortality risk has decreased and the leading cause of mortality has shifted to cancer, though cardiovascular comorbidities remain an important contributing factor in disease burden.[12] Current guidelines for diagnosis and treatment of acromegaly recommend assessment of cardiac function at baseline using echocardiography.[12] This includes biannual blood pressure measurements, and baseline echocardiography and electrocardiography (with annual reassessment in case of abnormalities at baseline).[12] Currently, there is no consensus on whether the current management of acromegaly is sufficient in reversing ACM.[13] Medical treatment for acromegaly with first-generation somatostatin receptor ligands (SRLs; eg, octreotide LAR or lanreotide ATG) resulting in biochemical remission may enhance cardiac function by improving diastolic function and decreasing volume overload.[13] Several studies have investigated the effect of both surgery and SRLs as primary GH-lowering treatment on cardiac indices, reporting varying results. In a study conducted by Gilbert et al.,[14] no significant improvement in systolic function or cardiac structure was found following primary medical therapy. These findings appear to be contradicted by a study by Colao et al.[15] where systolic function and cardiac structure improved following primary SRL therapy in a larger cohort. Similar contradicting results have been reported in studies investigating primary surgery for acromegaly.[16,17] However, the constellation of hypertension, cardiac arrhythmias, glucose intolerance, and diastolic dysfunction, which leads to heart failure may be incurable, especially in cases where GH levels remain uncontrolled for a prolonged period.[1,2] Therefore, adequate control of GH hypersecretion, hypertension, and heart disease may be essential to improve the ultimate mortality rates as a result from cardiac comorbidity. This systematic review aims to assess the effect of the first treatment for acromegaly on cardiac involvement.

Methods

Protocol registration and search strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and the Declaration of Helsinki (Table S1).[18] The protocol for this systematic review was registered on PROSPERO 2022 (PROSPERO ID: CRD42022368596). PubMed, Embase, Emcare, and Web of Science were systematically searched on February, 25, 2022 to identify all studies investigating the effect of acromegaly treatment (ie, GH and/or IGF-I reduction) on cardiomyopathy in acromegaly patients. The search terms consisted of keywords related to the patient population: "acromegaly"; the intervention: "somatostatin receptor ligands"/"dopamine agonists"/"radiotherapy"/"transsphenoidal surgery"; and the outcome: "heart"/"acromegalic cardiomyopathy" (Supplemental Material 1).

Study selection

All studies were independently screened on title and abstract by 2 reviewers (K.A.H. and J.K.M.A.). After this selection, the full text of these articles was studied. Inclusion criteria were: (1) studies should include patients with the diagnosis of acromegaly (elevated IGF-I concentration [corrected for sex and age] alone or combined with the failure to suppress on OGTT)[19] and had to report on the effect of a first intervention for acromegaly (ie, treatment-naive patients treated with a single treatment modality) on cardiac structure and/or function, (2) studies had to have at least one follow-up moment, and (3) studies had to be written in English. Exclusion criteria were: (1) studies that did not provide baseline (ie, treatment-naive patients) or postprimary treatment measurements, (2) results from conference papers and abstracts. In cases of disagreement, a consensus was negotiated.

Data extraction and quality assessment

After the full-text screening, the 2 reviewers (K.A.H. and J.K.M.A.) extracted data from the eligible articles independently using Microsoft Office Excel 2016. After data extraction, each reviewer verified the other reviewer's data entries. All study characteristics, patient characteristics, and (cardiac) outcome measurements that were relevant to the treatment of acromegaly were extracted. Duplicate records were identified following the guidelines of Bramer et al.[20] using Endnote X20 for Windows.

To assess the quality of the included studies, a modified Newcastle–Ottawa Scale (NOS) was used for longitudinal studies, and the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for case reports (Tables S2 and S3). Compliance with ≥75% of the criteria listed in the scale was viewed as low risk of bias, <50% compliance was considered as high risk of bias, and compliance between 50% and 75% as an intermediate risk of bias.

Statistical analysis

Given the heterogeneous nature of the cardiac outcome measurements of the retrieved studies, a meta-analysis was deemed not to be feasible and thus not performed. Therefore, results are presented as descriptive data. Unless otherwise stated, continuous variables are presented as mean with standard deviation (SD) or, if not normally distributed, as median with interquartile range (IQR). Categorical variables are presented as counts and percentages. All statistical analyses were performed using IBM SPSS 29.0 software (IBM Corp., Armonk, NY).

Results

Characteristics of included studies

A total of 2541 studies were identified from the searched databases. After removing duplicate records and initial screening

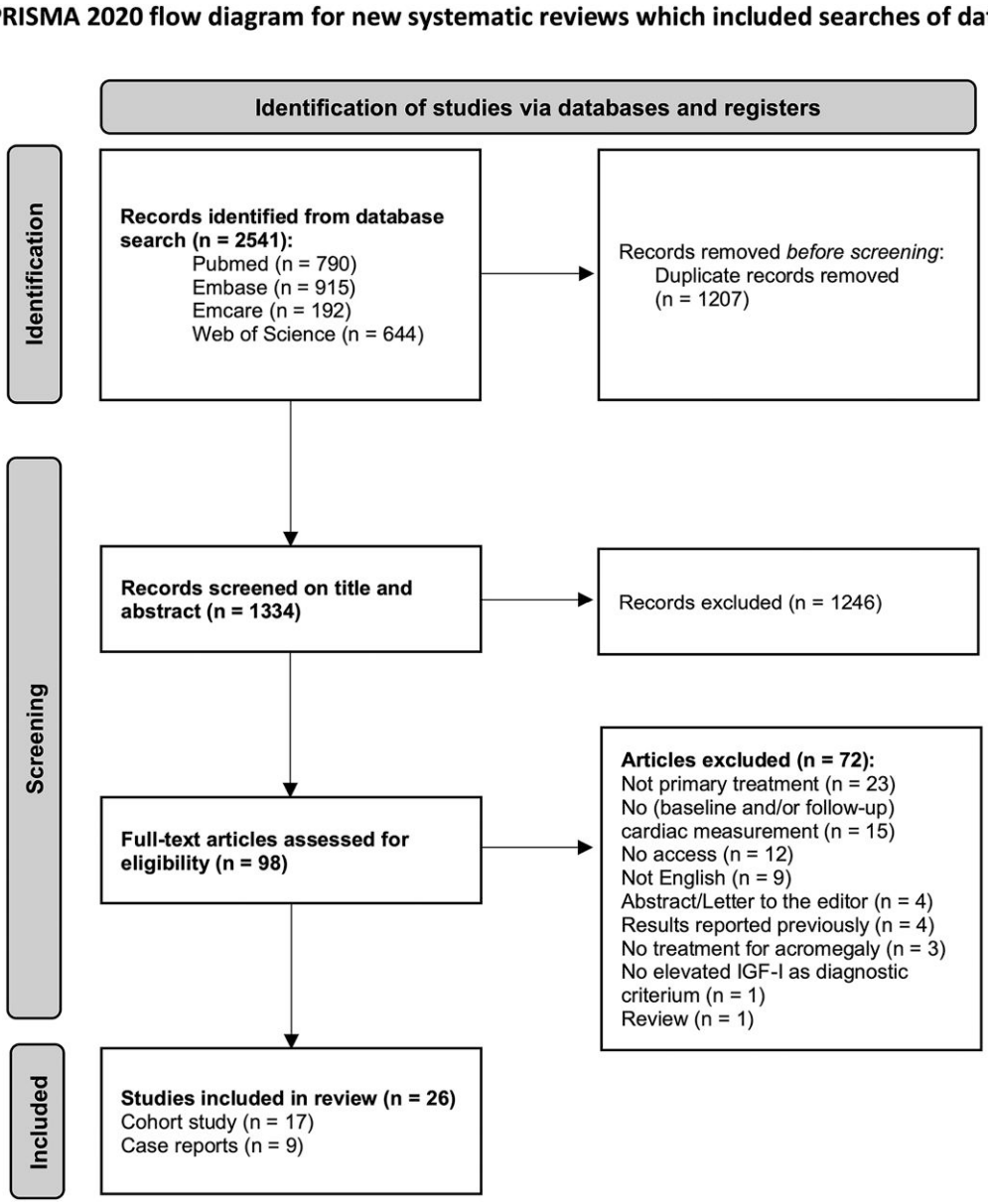

Figure 1. PRISMA flowchart of study selection and inclusion. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

of the title and abstract, full-text eligibility was assessed for 98 articles. Finally, 26 articles were included in this systematic review (Figure 1).[18] All studies received approval from their local independent ethical committee. Seventeen cohort studies investigated the effect of the first intervention on cardiac outcomes in treatment-naive acromegaly patients and 9 case reports reported the cardiac outcomes for individual patients.[14-17,21-42] Quality assessment using the modified NOS, and JBI Critical Appraisal Checklist for Case Reports demonstrated that none of the studies had a high risk of bias; 92.0% ($n = 24$) had a low risk of bias and 8.0% ($n = 2$; cohort studies) had an intermediate risk of bias (Tables S3 and S4).

Investigated therapies

The primary treatment consisted of first-generation SRLs in 9, and surgery in 6 cohort studies (Figure 2). Two cohort studies investigated both first-generation SRLs and surgery as treatment (Figure 2). First-generation SRLs duration ranged from 3 to 63 months in these studies (Table S2). In 8 case reports the treatment modality was first-generation SRLs and surgery in one case (Figure 2). Follow-up time ranged from 2 weeks to 5 years across all studies (Table S2).

Cohort studies

Baseline patient characteristics

The baseline patient characteristics are listed in Table 1 for all included studies. The mean age ranged from 31.2 to 58.0 years across the 17 cohort studies (Table 1). Almost all included studies demonstrated a balanced sex distribution among patients. All studies showed a decrease in serum GH and IGF-I levels following treatment, though not all were statistically significant; IGF-I levels prior to treatment ranged 69.8-120.1 nmol/L decreased to a range of 28.5-76.9 nmol/L following treatment. Cardiac outcome measures were divided in cardiac structure and cardiac

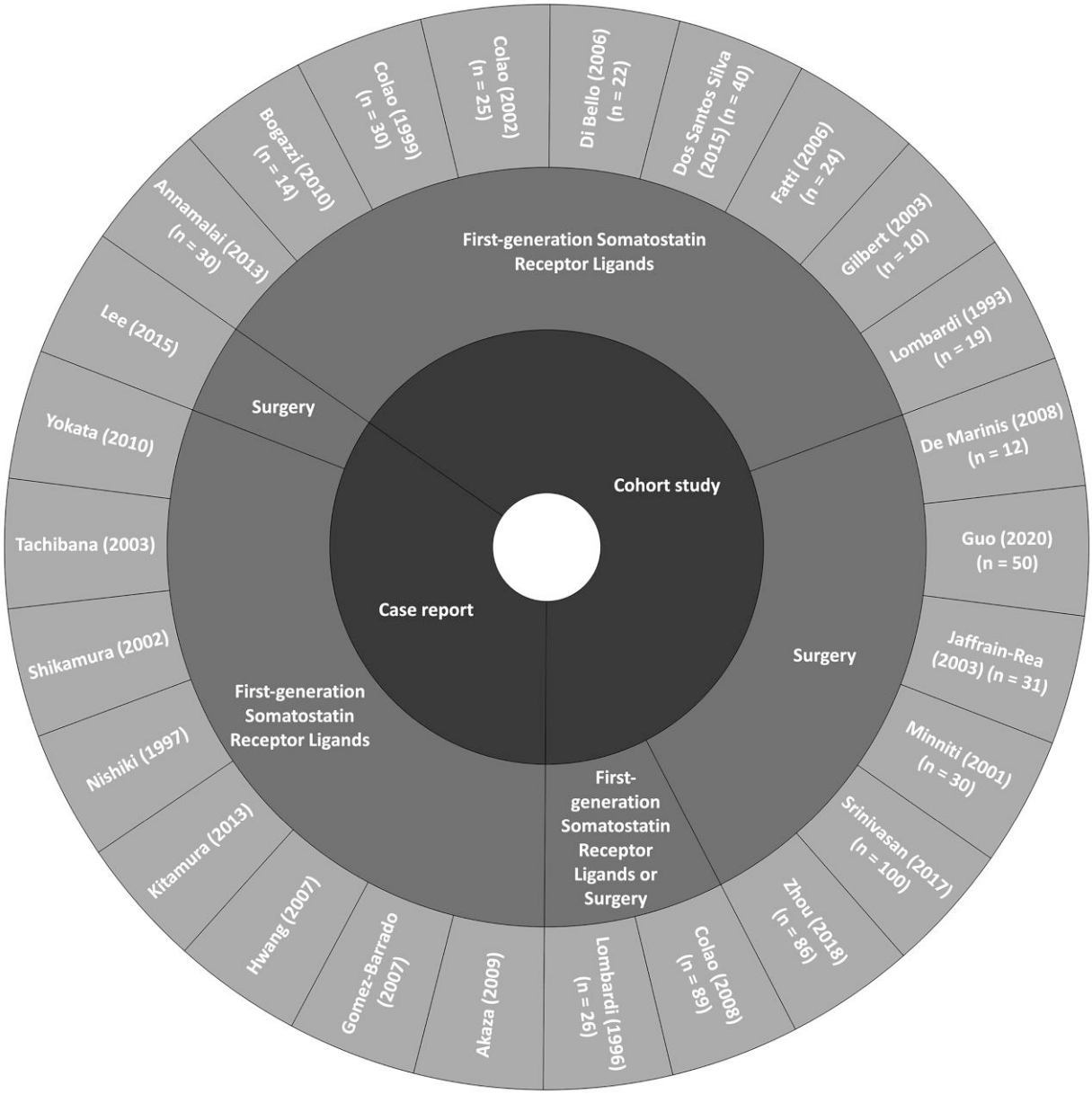

Figure 2. Pie chart of all included studies divided by study design and investigated treatment modality.

function. The cardiac structure was assessed using the proportion of patients with left ventricle hypertrophy (LVH) and the mean (indexed) left ventricular mass (LVM and LVMi). With regards to cardiac function, the left ventricular ejection fraction (LVEF) was used to evaluate the left ventricular systolic function, and the E/A ratio was used to evaluate the left ventricle diastolic function. Prior to treatment, across all studies the median mean LVEF was 60% (range 49%-78%); E/A ratio 0.98 (range 0.6-1.4); LVM 220.7 g (range 104-274) g; LVMi 126.5 g/m2 (56.0-152.5 g/m^2) (Figures 3 and 4, Tables 2 and 3).

Cardiac structure outcomes after intervention

Thirteen out of 17 studies determined the proportion of patients with LVH with criteria based on LVM/LVMi.[14-16,21,22,24,26,28-33] Seven studies defined LVH for men as LVMI ≥ 135 g/m^2 and for women as LVMI ≥ 110 g/m^2.[15,16,24,26,28,30,31] Bogazzi et al.[22] used LVMi ≥ 125 g/m^2 as the definition of LVH for men. Annamalai et al.[21] classified LVH in mild, moderate, and severe, with mild starting from 103 g/m^2 for men and 89 g/m^2 for women. The remaining 4 studies gave no definition of LVH.[14,27,32,33] All studies reported a decrease in the proportion of patients with LVH, while this decrease was only statistically significant in 3 studies (Table 2).[16,22,24] Overall, the median proportion of patients with LVH decreased following treatment from 65.0% (range 7.5%-100.0%) to 27.1% (range 3.5%-60.6%) (median Δ −27.6; range −57.8 to −2.7) (Figure 3, Table 3). Concordantly, the median mean LVM and LVMi reduced following treatment from 220.7 g (range 104.0-274.0 g) to 184.0 g (123.0-276.0 g) (median Δ −25.6; range −40.6-2.0) and from 126.5 g/m^2 (range 56.0-152.5 g/m^2) to 109.1 g/m^2 (range 59.6-134.1 g/m^2) (median Δ −16.4; range −35.6 to −1.9), respectively (Figure 3, Table 3). Of all studies reporting LVM/LVMi ($n = 15$), 11 studies used the Devereux formula (or a variation thereof) to calculate LVM/LVMi

Table 1. Baseline patient characteristics of included studies and case reports.

Author and ref.		Year	N	Treatment scheme	Age	Sex (M/F)	HT (%)	HF (%)	DM (%)	Serum IGF-I (nmol/L)	
										at baseline	At follow-up
Annamalai, A. K., et al.[21]		2013	30	Lanreotide 60-120 mg/28 days/	54 (12)	15 (50.0%)/15 (50.5%)	15 (50.0%)		8 (26.7%)	Decreased after treatment	
Bogazzi, F., et al.[22]		2010	14	Lanreotide 120 mg/28 days	57 (12)	6 (42.9%)/8 (57.1%)	8 (57.1%)		6 (42.9%)	95.0 (27.8)	52.5 (21.1)
Colao, A., et al.[23]		1999	30	Octreotide 0.05-0.1 mg/ 3× per day	58 (12)	15 (50.0%)/15 (50.0%)	6 (20.0%)			**88.1 (23.0)**	**52.2 (27.3)**
	BR (n = 13)				59 (12)						
	PD (n = 17)				60 (12)						
Colao, A., et al.[15]		2002	25	Octreotide-LAR 20-30 mg/28 days	31.2 (6.0)	12 (48%)/13 (52%)					
	Disease duration <5 (n = 15)									**99.5 (23.0)**	**56.0 (13.0)**
	Disease duration >5 (n = 10)									**103.6 (23.4)**	**54.3 (14.8)**
Di Bello, V., et al.[25]		2006	22	Octreotide-LAR 20 mg/28 days	50.1 (10.3)	13 (59.1%)/9 (40.9%)	0 (0.0%)		0 (0.0%)	**86.4 (38.2)**	**30.3 (12.0)**
Dos Santos Silva, C. M., et al.[26]		2015	40	Octreotide-LAR 20-30 mg/28 days	44.5 (13.6)	22 (55.0%)/18 (45.0%)	22 (55.0%)		10 (25.0%)	12 patients achieved biochemical remission	
Fatti, L. M., et al.[27]		2006	24	Octreotide-LAR 20-30 mg/28 days/ Lanreotide 60 mg/28 days/ Octreotide 300 µg/daily	51.2 (12.2)	9 (37.5%)/15 (62.5%)	14 (58.3%)		3 (12.5%)		
Gilbert, J., et al.[14]		2003	10	Octreotide-LAR 20-30 mg/28 days	52.2 (11.4)	6 (60.0%)/4 (40.0%)				115.9 (68.9)	77.1 (32.1)
Lombardi, G., et al.[30]		2002	19	Lanreotide 30 mg/14 days	41.7 (11.4)	9 (47.4%)/10 (52.6%)				113.4 (43.3)	
	BR (n = 11)									**108.3 (26.1)**	**50.8 (28.2)**
	PD (n = 8)									**120.4 (61.1)**	**75.3 (35.2)**
De Marinis, L., et al.[16]		2008	12	Surgery	54.6 (14.9)	5 (41.7%)/7 (58.3%)				**707.2 (328.1)**	**92.6 (43.0)**
Guo, X., et al.[17]		2020	50	Surgery	41.6 (12.8)	27 (54.0%)/23 (46.0%)					
	BR (n = 24)										
	PD (n = 21)										
Jaffrain-Rea, M.-L., et al.[28]		2003	31	Surgery	48.1 (11.2)	16 (51.6%)/15 (48.4%)	11 (35.5%)		3 (9.7%)	85.9 (18.4)	28.6 (2.4)
Minniti, G., et al.[31]		2001	30	Surgery	46 (12.0)	17 (56.7%)/13 (43.3%)					
	BR (n = 15)				45 (9.7)	9 (60.0%)/6 (40.0%)				72.1 (19.3)	Normalized
	PD (n = 15)				46 (12.8)	8 (53.3%)/7 (46.7%)				73.4 (17.4)	59.4 (16.1)
Srinivasan, A., et al.[32]		2017	100	Surgery							

(*continued*)

Table 1. Continued

Author and ref.		Year	N	Treatment scheme	Age	Sex (M/F)	HT (%)	HF (%)	DM (%)	Serum IGF-I (nmol/L)	
										at baseline	At follow-up
	Prospective (n = 38)				38.8 (11.9)	21 (55.3%)/17 (44.7%)	7 (18.4%)		5 (13.2%)		
	Retrospective (n = 62)				39.6 (10.5)	28 (45.2%)/34 (54.8%)	12 (19.3%)		18 (29%)		
Zhou, H., et al.[33]		2018	86	Surgery	42.6 (5.5)	45 (52.3%)/41 (47.7%)	25 (29.0%)	16 (18.6%)			
Colao, A., et al.[24]		2008	89	Octreotide-LAR 10-40 mg/28 days/ Lanreotide 30-120 mg/28 days/Surgery							
	First-line SRL (n = 56)				49 (18)	28 (50.0%)/28 (50.0%)	33 (58.9%)		7 (12.5%)	93.3 (29.5)	
	First-line TSS (n = 33)				51 (17)	14 (42.4%)/19 (57.6%)	18 (54.6%)		3 (9.1%)	88.8 (32.6)	
Lombardi, G., et al.[29]		1996	18[a]	Surgery/ Octreotide 0.15-0.6 mg/ daily	45.0 (12.8)	11 (42.3)/15 (57.7%)				70.0 (29.1) at baseline; In long-term octreotide patients from 100.5 (9.5) to 30.8 (1.3)	
Akaza, I., et al.[34]		2009	1	Octreotide 0.2 mg/daily	59	M	Yes			144.1	42.7
Gomez-Barrado, J. J., et al.[35]		2007	1	SRL	61	F			Yes		
Hwang, M.-W., et al.[36]		2007	1	Octreotide 0.1 mg/daily (discontinued after 8 weeks)	42	M	Yes				21.9
Kitamura, T., et al.[37]		2013	1	Octreotide-LAR 20 mg/28 days	56	M	Yes			40.2	
Lee, H. M., et al.[38]		2015	1	Surgery	47	F	Yes		Yes	24.1	32.7
Nishiki, M., et al.[39]		1997	1	Octreotide 0.24 mg/daily	68	F	Yes			53.7 (2.6)	18.3 (2.4)
Shimakura, A., et al.[40]		2002	1	Octreotide 0.3 mg/daily	43	M	Yes			191.2	146.7
Tachibana, H., et al.[41]		2003	1	Octreotide 0.3 mg/daily	46	M	Yes		Yes	111.4	41.9
Yokota, F., et al.[42]		2010	1	Octreotide-LAR 30 mg/28 days	51	M				66.0 at baseline; Above reference range following treatment	

Abbreviations: HT, hypertension; HF, heart failure; DM, diabetes mellitus; BR, biochemical remission; PD, persistent disease; SRL, somatostatin receptor ligand; TSS, transsphenoidal surgery.
[a]A total of 26 patients were initially included, but cardiac outcome data has only been presented for 18 patients. Data presented in bold represent statistically significant difference at follow-up from baseline with P-value < .05.

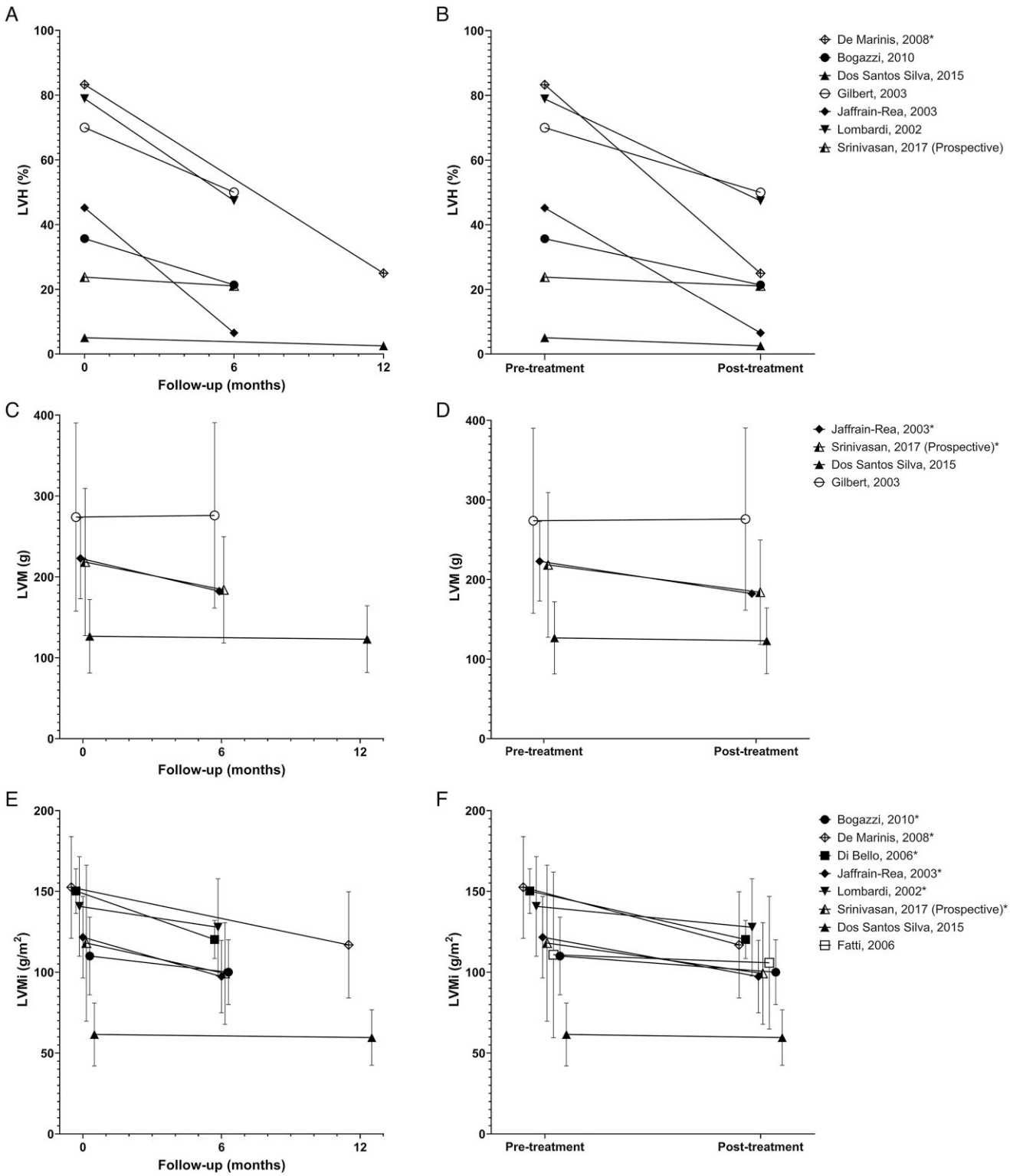

Figure 3. Cardiac dimensions at baseline and following primary treatment for acromegaly. (A) The proportion of LVH over time, (C) the mean LVM, and (E) the mean LVMi. (B, D, F) The proportion of LVH, mean LVM, and mean LVMi before and after treatment including studies without a uniform follow-up time for each patient. The error bars represent the standard deviation of the reported outcome. **P*-value < .05. LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVMi, indexed left ventricular mass.

(Table S2).[14-16,21,24,26-31] Four studies did not report the method for calculating LVM/LVMi.[22,25,32,33] All 15 studies reported a decrease in LVMi/LVM, while only in 9 studies this decrease was significantly lower compared to the baseline (Table 2).[15,16,22,24,25,28,30-32]

Cardiac function outcomes after intervention

Overall, the median mean EF changed from 60.2% (range 49.2%-77.8%) to 59.8% (53.3%-80.3%) (median Δ −2.5; range −1.90-6.7) following treatment (Figure 4, Table 3). Nine of the 14 studies reporting LVEF showed an increase in

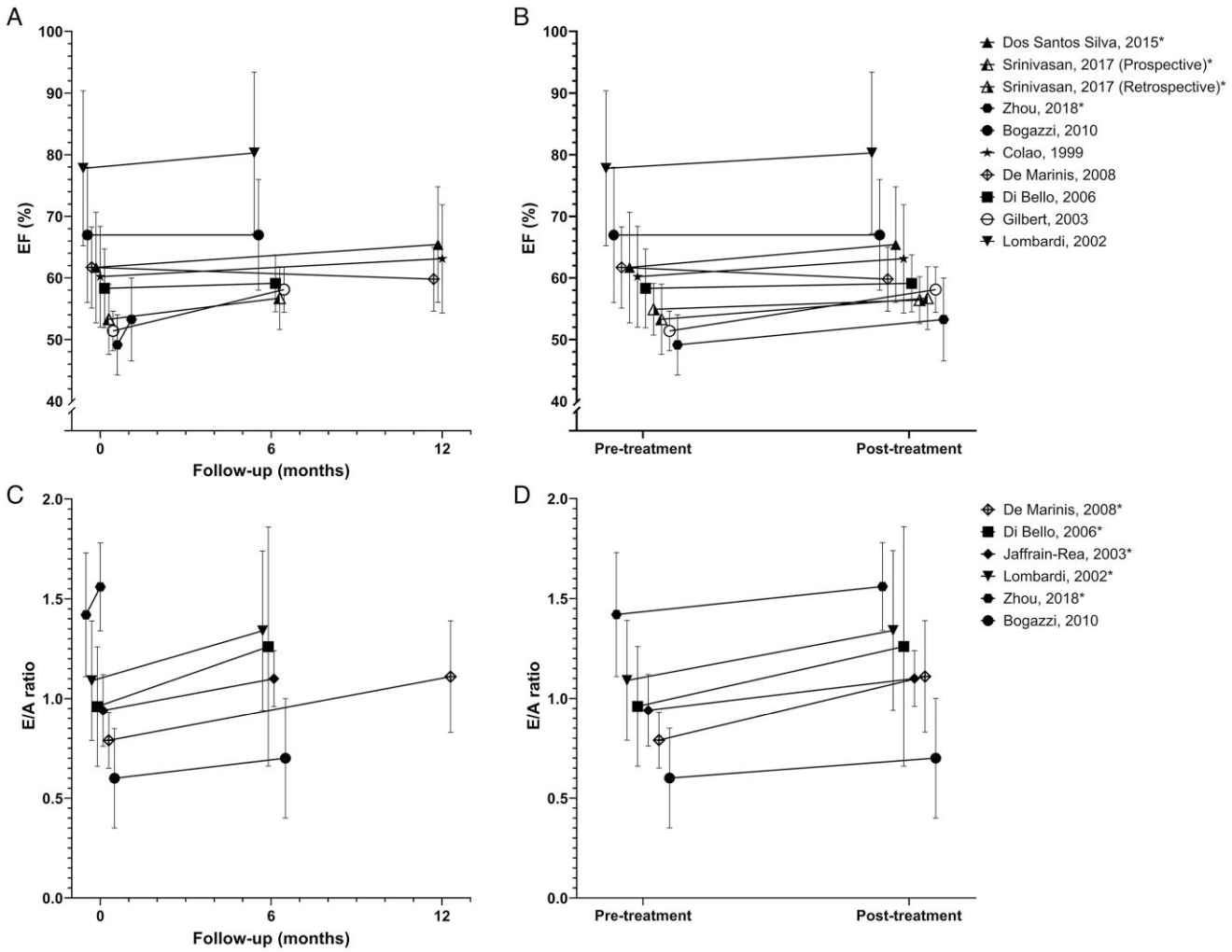

Figure 4. Cardiac function at baseline and following primary treatment for acromegaly. (A) The mean EF over time, and (C) the mean E/A ratio. (B, D) The mean EF and mean E/A ratio before and after treatment including studies without a uniform follow-up time for each patient. The error bars represent the standard deviation of the reported outcome. **P*-value < .05. EF, left ventricular ejection fraction; E/A ratio, ratio of the early (E) to late (A) ventricular filling velocities.

LVEF following treatment (Figure 4, Table 2).[14,23,25,26,29-33] The study by De Marinis et al.[16] showed a decrease in LVEF after surgery. Similarly, in a study from Colao and colleagues in 2008 only the group treated with first-generation SRLs showed a significant increase in LVEF.[24] In the study of Colao and colleagues from 2002, the subgroup with a disease duration <5 years also had a decrease in LVEF, while the subgroup with a disease duration >5 years showed an increase.[15] Bogazzi and colleagues showed a LVEF which neither increased nor decreased.[22] Across all 7 studies reporting E/A ratio, the median mean E/A ratio increased from 0.98 (range 0.60-1.42) to 1.11 (range 0.70-1.56) (median Δ 0.15; range 0.5-0.32) following treatment (Figure 4, Table 3). An E/A ratio of 0.75-1.5 indicates a normal diastolic function, while a reduced E/A ratio is suggestive of impaired myocardial relaxation and an increased E/A ratio of restrictive filling.[43]

Relation with biochemical remission

Two included studies described the difference in cardiac structure between a group that achieved biochemical control and a group that did not achieve biochemical control (Figure S1, Table 2). Minniti et al.[31] demonstrated that LVMi significantly decreased following treatment in patients that attained biochemical remission ($n = 15$), but not in those with persistent disease ($n = 15$). Lombardi et al.[30] report that the LVMi is significantly decreased in both groups ($n = 19$). Four studies reported the difference in LVEF between the group that achieved control and the group that had persistent disease (Figure S2, Table 2).[17,23,30,31] Three of these reported that the LVEF increased following treatment, though only the study by Colao et al.[23] demonstrated a statistically significant increase in LVEF in the group that achieved biochemical control ($n = 13$). Guo et al.[17] observed a decrease in LVEF following treatment in the subgroup with biochemical remission ($n = 24$), while Colao et al.[23] measured a decrease in the subgroup without biochemical remission ($n = 17$). The study by Lombardi et al.[30] also investigated the E/A ratio and reported a significant increase in E/A ratio following treatment in the group with biochemical remission ($n = 11$). Dos Santos Silva et al.[26] reported no difference in LVMi or LVEF between those that achieved biochemical remission and those with persistent disease, although absolute values were not provided.

Table 2. Reported structural and functional cardiac outcome measures of included studies and case reports.

Author and ref.		Year	Cardiac imaging	EF (%)		E/A ratio		LVH (%)		LVM (g)		LVMi (g/m^2)	
				At baseline	At follow-up	At baseline	At follow-up	At baseline	At follow-up	At baseline	At follow-up	At baseline	At follow-up
Annamalai, A. K., et al.[21]		2013	EC					14 (46.7%)				Reduced in men after lanreotide, but not in women; paradoxical rise in 5 women from normal to LVH	
Bogazzi, F., et al.[22]		2010	CMRI	67 (11)	67 (9)	0.6 (0.25)	0.7 (0.3)	**10 (71.4%)**	**4 (28.6%)**			77 (9)	70 (11)
Colao, A., et al.[23]		1999	CS	60.2 (8.2)	63.1 (8.8)								
	BR (n = 13)			**56.5 (6.5)**	**66.5 (7.9)**								
	PD (n = 17)			63.1 (7.8)	60.2 (7.8)								
Colao, A., et al.[15]		2002	EC	60.1 (6.5)				15 (60%)				131.2 (16.5)	
	Disease duration <5 (n = 15)			**63.6 (3.9)**	**59.9 (3.1)**							**128.9 (17.8)**	**104.4 (12.8)**
	Disease duration >5 (n = 10)			**54.9 (6.6)**	**60.7 (5.4)**							**134.6 (13.9)**	**113.9 (17.1)**
Di Bello, V., et al.[25]		2006	EC	58.3 (6.4)	59.1 (4.6)	**0.96 (0.3)**	**1.26 (0.6)**					**150.2 (13.9)**	**120.2 (11.8)**
Dos Santos Silva, C. M., et al.[26]		2015	CMRI	**61.7 (9.0)**	**65.4 (9.4)**			2 (7.5%)	1 (3.5%)	126.6 (45.4)	123.0 (41.3)	61.5 (19.5)	59.6 (17.2)
Fatti, L. M., et al.[27]		2006	EC									110.8 (51.3)	105.8 (41.0)
Gilbert, J., et al.[14]		2003	EC	51.4 (3.2)	58.1 (3.7)			7 (70%)	5 (50%)	274.0 (116.3)	276.0 (114.5)		
Lombardi, G., et al.[30]		2002	EC	77.8 (12.6)	80.3 (13.1)	**1.09 (0.3)**	**1.34 (0.4)**	15 (78.9%)	9 (47.4%)			**140.7 (30.9)**	**127.8 (30.1)**
	BR (n = 11)			77 (13.3)	82 (13.3)	**1.0 (0.3)**	**1.2 (0.3)**					**138 (33.2)**	**123 (29.8)**
	PD (n = 8)			78 (14.1)	78 (14.1)	1.2 (0.3)	1.5 (0.6)					**144 (28.3)**	**134 (31.1)**
De Marinis, L., et al.[16]		2008	EC	61.7 (6.6)	59.8 (5.2)	**0.79 (0.14)**	**1.11 (0.28)**	**10 (83.3%)**	**3 (25.0%)**			**152.5 (31.5)**	**116.9 (32.9)**
Guo, X., et al.[17]		2020	CMRI	62.0 (5.8)						104 (32)		56 (15)	
	BR (n = 24)			63.3 (5.2)	62.5 (5.7)								
	PD (n = 21)			60.5 (6.4)	61.3 (4.8)								
Jaffrain-Rea, M.-L., et al.[28]		2003	EC			**0.94 (0.18)**	**1.10 (0.14)**	14 (45.2%)	2 (6.5%)	**222.9 (49.9)**	**182.3 (4.2)**	**121.6 (25.2)**	**97.3 (22.4)**
Minniti, G., et al.[31]		2001	EC										
	BR (n = 15)			71.3 (13.2)	72.9 (11.2)			9 (60.0%)	1 (6.7%)	**238.6 (58.1)**	**198.4 (50.3)**	**127.1 (29.8)**	**104.4 (25.6)**
	PD (n = 15)			70.9 (12.4)	74.5 (8.5)			6 (40.0%)	6 (40.0%)	227.7 (56.9)	216.7 (78.6)	120.8 (24.8)	115.6 (34.5)
Srinivasan, A., et al.[32]		2017	EC										
	Prospective (n = 38)			**53.3 (5.7)**	**56.7 (5.1)**			9 (23.8%)	8 (21.1%)	**218.4 (91)**	**184 (65.7)**	**118 (48.3)**	**99.2 (31.4)**
	Nadir GH <1 ng/mL			**55.3 (5.2)**	**58.1 (5.8)**					**181.8 (52.1)**	**153.7 (43.2)**	**98.6 (26.1)**	**85.3 (21.7)**
	1-5 ng/mL			**52.7 (6.5)**	**56.3 (4.8)**					**242.3 (112)**	**196.1 (71)**	**129.2 (57.3)**	**107.5 (38.4)**
	>5 ng/mL			51.6 (4.2)	54 (6.5)					218 (63.8)	214 (76.88)	118 (32.8)	116.9 (38.1)
	Retrospective (n = 62)			**54.9 (4.17)**	**56.4 (3.8)**								
	Nadir GH <1 ng/mL			**56.1 (1.8)**	**57.8 (2.4)**								
	1-5 ng/mL			**54.7 (4.7)**	**56.3 (4.1)**								
	>5 ng/mL			51.3 (5.5)	52 (5.2)								
Zhou, H., et al.[33]		2018	EC	**49.15 (4.89)**	**53.26 (6.73)**	**1.42 (0.31)**	**1.56 (0.22)**	86 (100%)					

(*continued*)

Table 2. Continued

Author and ref.		Year	Cardiac imaging	EF (%)		E/A ratio		LVH (%)		LVM (g)		LVMi (g/m^2)	
				At baseline	At follow-up	At baseline	At follow-up	At baseline	At follow-up	At baseline	At follow-up	At baseline	At follow-up
Colao, A., et al.[24]		2008	EC										
	First-line SRL (n = 56)			**55.3 (9.2)**	**58.0 (6.4)**	**1.00 (0.22)**	**1.11 (0.15)**	**41 (73.2%)**	**25 (44.6%)**			**144.4 (36.1)**	**125.2 (32.2)**
	First-line TSS (n = 33)			56.4 (10.3)	55.2 (6.6)	**1.00 (0.18)**	**1.05 (0.13)**	28 (84.8%)	20 (60.6%)			**146.1 (35.3)**	**134.1 (32.3)**
Lombardi, G., et al.[29]		1996	CS and EC	62.0 (9.0) at baseline; Significantly increased following surgery (n = 8), but not following long-term OCT				4 (15.4%)		Significantly reduced after 6 months of OCT		129.0 (33.0) at baseline; Significantly reduced after 6 months of OCT	
Akaza, I., et al.[34]		2009	EC	28	54	0.53	1.05	Yes					
Gomez-Barrado, J. J., et al.[35]		2007	EC	22	56								
Hwang, M.-W., et al.[36]		2007	EC	21	56								
Kitamura, T., et al.[37]		2013	EC	28.5	49.0	0.69	0.96	Yes					
Lee, H. M., et al.[38]		2015	EC	25	73			Yes				252.8	96.75
Nishiki, M., et al.[39]		1997	EC	29	76			Yes		425	212		
Shimakura, A., et al.[40]		2002	EC	11	27	0.79	0.89			591	368		
Tachibana, H., et al.[41]		2003	EC	38	50			Yes					
Yokota, F., et al.[42]		2010	EC	11	20								

Data presented in bold represent statistically significant difference at follow-up from baseline with P-value < .05.
Abbreviations: EC, echocardiography; CMRI, cardiac magnetic resonance imaging; CS, cardiac scintigraphy; EF, left ventricular ejection fraction; E/A ratio, ratio of the early (E) to late (A) ventricular filling velocities; LVM, left ventricular mass; LVMi, indexed left ventricular mass; LVH, left ventricular hypertrophy; BR, biochemical remission; PD, persistent disease; SRL, somatostatin receptor ligand; TSS, transsphenoidal surgery; OCT, octreotide.

Table 3. Summary of reported results on structural and cardiac outcome measures of included cohort studies.

	Studies (*n*)	At baseline	At follow-up	Missing outcome data (*n*)	Median calculated Δ (range)
All studies ($n = 17$)					
Median mean EF (range), %	14	60.2 (49.2-77.8)	59.8 (53.3-80.3)	1	2.5 (−1.90-6.7)
Median mean E/A ratio (range)	7	0.98 (0.60-1.42)	1.11 (0.70-1.56)	0	0.15 (0.5-0.32)
Median proportion of patients with LVH (range), %	13	65.0 (7.5-100.0)	27.1 (3.5-60.6)	4	−27.6 (−57.8 to 2.7)
Median mean LVM (range), g	6	220.7 (104.0-274.0)	184.0 (123.0-276.0)	1	−25.6 (−40.6-2.0)
Median mean LVMi (range), g/m^2	13	126.5 (56.0-152.5)	109.1 (59.6-134.1)	2	−16.4 (−35.6 to 1.9)
Medication studies ($n = 11$)[a]					
Median mean EF (range), %	9	60.2 (51.4-77.8)	61.7 (58.0-80.3)	1	2.6 (0.0-6.7)
Median mean E/A ratio (range)	4	0.98 (0.60-1.09)	1.19 (0.70-1.34)	0	0.18 (0.10-0.30)
Median % of patients with LVH (range)	8	65.0 (7.5-78.9)	44.6 (3.5-50.0)	3	−28.6 (−42.8 to 4.0)
Median mean LVM (range), g	2	200.3 (126.6-274.0)	199.5 (123.0-276.0)	0	−0.8 (−3.6-2.0)
Median mean LVMi (range), g/m^2	8	130.1 (61.5-150.2)	108.2 (59.6-127.8)	1	−12.9 (−30.0 to 1.9)
Surgery studies ($n = 7$)[a]					
Median mean EF (range), %	6	56.4 (49.2-71.1)	56.7 (53.3-73.7)	0	1.5 (−1.9-4.1)
Median mean E/A ratio (range)	4	0.97 (0.79-1.42)	1.11 (1.05-1.56)	0	0.15 (0.05-0.32)
Median % of patients with LVH (range)	6	66.7 (23.8-100.0)	23.3 (6.5-60.6)	1	−26.7 (−57.8 to −2.7)
Median mean LVM (range), g	4	220.7(104.0-233.2)	184.0 (182.3-207.6)	1	−34.4 (−40.6 to −25.6)
Median mean LVMi (range), g/m^2	6	122.8 (56.0-152.5)	110.0 (97.3-134.1)	1	−18.8 (−35.6 to −12.0)

Abbreviations: EF, left ventricular ejection fraction; E/A ratio, ratio of the early (E) to late (A) ventricular filling velocities; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVMi, indexed left ventricular mass; Δ, difference.
[a]One study has been included in both subgroup analyses due to its separate reporting of outcomes for patients treated with primary medical therapy and those with primary surgery.

Impact of treatment modality on outcomes

Of all studies, one relatively large study by Colao et al.[24] directly compared first-generation SRLs ($n = 56$) to first-line surgery ($n = 33$), measured cardiac outcomes did not differ (Table 2). No large disparity in median outcomes between studies investigating primary surgery and studies investigating first-generation SRLs was present (Tables 1-3, Figures S3-S6).

Case reports

Age ranged from 42 to 68 years across all case reports and 6 out of the 9 patients were male (Table 1). Eight patients were treated with first-generation SRLs ranging from 6 weeks to 14 months.[34-37,39-42] All cases demonstrated moderate to severe systolic dysfunction based on LVEF prior to treatment (Table 2). All case reports showed an increased LVEF following treatment, 7 patients demonstrated recovery of LVEF to (near) normal function (Table 2, Figures S7-S10)[34-39,41] The significant improvement in LVEF in the patient reported by Lee et al.[38] was attributed to successful antihypertensive treatment, not surgical treatment for acromegaly.

Discussion

To our knowledge, this is the first systematic review focusing the effects of first intervention of acromegaly on cardiac parameters. The results presented in this systematic review indicate that first intervention with surgery or first-generation SRLs for acromegaly appear to improve disease-associated structural and functional cardiac alterations.

Cardiac outcomes

In this systematic review, the most pronounced improvement in acromegaly-associated cardiac involvement is seen in the reduction of LVM/LVMi and consequently the proportion of patients with LVH. Left ventricular mass/left ventricular mass index have been reported as an independent predictor of cardiovascular risk, where a decrease of 25.3 g/m^2 in LVMi is reported to correspond with a reduction of 38% of adverse cardiovascular outcomes and 28% of all-cause mortality.[44] Despite the improvements of LVM/LVMi, cardiac function remained unchanged. In current literature, patients with mild diastolic dysfunction (E/A ratio < 0.75) and severe diastolic dysfunction (E/A ratio > 1.5) are reported to have a higher 5-year mortality rate when compared to patients with normal diastolic function (5.6% and 8.0% vs. 2.9%, respectively).[45] Interestingly, in a study by Kuhn et al.,[46] patients with LVEF ≤60% at baseline demonstrated a significant increase in LVEF, while patients with LVEF >70% at baseline had a significant decrease after long-term pegvisomant (ie, a growth hormone receptor antagonist). In this study, the majority patients already received one or more treatments for acromegaly prior to start on pegvisomant; 76.2% had prior surgery, 16.7% radiotherapy, 95.2% SRLs, and 50.0% cabergoline.[46] The seemingly paradoxical outcome in cardiac function may be explained by the natural stratification on ACM stage in the statistical analysis of this study. Both patients with ACM-related hyperkinetic syndrome (ie, LVEF >70%) and patients with systolic dysfunction (ie, LVEF ≤60%) demonstrated improvement in cardiac function, respectively.[46]

Differences in outcome between treatment modalities

Currently, sufficient evidence to accurately determine changes in cardiac outcomes in acromegaly patients between the 2 first-line treatment modalities or different remission stages is lacking. Of all included studies, only Colao et al.[24] directly compared first-line first-generation SRLs with first-line surgery, where both groups achieved a comparable reduction of IGF-I levels (SRL: 2.38 ± 0.88 to 0.70 ± 0.17 [ULN]; surgery:

2.42 ± 1.05 to 0.80 ± 0.18 [ULN]). Here, LVMi and E/A ratio decreased significantly in both treatment arms, though LVEF significantly increased only following primary first-generation SRLs.

Biochemical remission

Only 4 studies have compared the cardiac outcomes between acromegaly patients achieving biochemical remission and those that did not.[17,23,30,31] Minniti et al.[31] and Lombardi et al.[30] hint toward greater improvement in cardiac structure with biochemical remission. All studies suggest that systolic and diastolic function improve more in patients that achieve biochemical remission, though not all results were statistically significant.[17,23,30,31] This is potentially the result of the relatively small study population with less than 50 participants in each study.[17,23,30,31] Moreover, Lombardi et al.[30] only included uncomplicated acromegaly patients, omitting the effect of treatment on patients with overt cardiac complications. Normalization of IGF-I levels is reported to significantly improve systolic blood pressure.[28,47] Furthermore, impaired glucose tolerance, a hallmark of disease activity in acromegaly, has been shown to resolve following successful normalization of GH/IGF-I excess.[48,49] Successful treatment of acromegaly also results in an improvement in lipid profile; an increase in high-density lipoprotein (HDL) cholesterol, and decrease in low-density lipoprotein (LDL) and triglyceride is witnessed.[50] Achieving biochemical remission as definitive treatment goal for acromegaly could therefore be essential in ameliorating the classical cardiometabolic risk profile of acromegaly patients and prevent adverse cardiac outcomes.

Other medical therapies

This review focused on the effect of first-line treatment-naive acromegaly patients on cardiac parameters. However, several studies have been performed investigating the cardiac outcomes with pegvisomant as second or third-line therapy, highlighting its promising effects on ACM. Over the last decade, pegvisomant has become an established effective and safe treatment option for acromegaly.[51] The large-scale, global, multicenter ACROSTUDY has reported that in 53.7% of patients IGF-I normalized after 1 year of treatment with pegvisomant, and 75.4% after 10 years, respectively, appearing superior to the traditional IGF-I normalization rates reported around 50% for first-generation SRLs.[52] Pivonello et al.[53] reported a significant reduction in LVMi, prevalence of LVH and improvement of LVEF and E/A ratio following 18 months of pegvisomant in a small cohort of 12 patients. Kuhn et al.[46] corroborated these findings in long-term treatment with pegvisomant, which improved systolic dysfunction and hyperkinetic syndrome. Additionally, LVMi significantly decreased following treatment, especially in those with severe LVH, and other cardiometabolic factors were also ameliorated.[46] An improvement of LVEF, E/A ratio, and LVMi after 60 months of combined pegvisomant and first-generation SRLs in patients resistant to long-term SRL monotherapy was demonstrated in a study by Auriemma et al.[54] To date no studies have specifically investigated the role of dopamine agonists (ie, cabergoline or bromocriptine) or second-generation SRLs (ie, pasireotide) in treating functional and structural cardiac changes in acromegaly.

Impact of disease duration

The early natural course of acromegalic heart disease has not yet been crystallized, potentially as a result of diagnostic delay impeding adequate scientific investigation thereof.[10] The study by Colao et al.[15] has shown that a short disease duration (ie, < 5 years) already negatively impacts cardiac performance, as opposed to the natural history of ACM previously postulated by Saccà et al.[10] where it is hypothesized that overt cardiac impairments only tend to develop in later stages of acromegaly.

Limitations

This study has potential limitations. Included studies may possibly be (somewhat) outdated, though not necessarily paired with higher risk of bias. Studies that reported on combined treatments for acromegaly (eg, combined effect of primary first-generation SRLs with subsequent surgery or treatment of non-naive cases) were excluded to determine a more unbiased outcome of a singular treatment. This review has therefore not focused on the effect of treatment in refractory acromegaly cases, who are more likely to have developed cardiovascular complications due to prolonged exposure to elevated GH/IGF-I levels. Selection bias in the cohort studies cannot be ruled out, since patients have not been randomized in included studies. However, many studies have excluded patients with overt heart failure requiring treatment, and patients in both the SRL and surgery cohorts presented with similar IGF-I levels and cardiac (dys)function at baseline. The SRL and surgery cohorts are comparable at baseline, and primary SRL therapy was therefore not reserved for the most severe acromegaly cases or cases with irresectable tumors. So, contraindication to surgery is not likely a cause of bias in these studies. Yet, confounding by indication cannot be completely ruled out. Furthermore, the included studies have not provided a clear overview of the use of cardiac medication in their study population. The role of cardiac medication in the observed changes in cardiac indices could therefore not be completely ruled out. Evidence presented here was focused on the treatment of naive patients and may therefore not provide sufficient insight into the expected treatment effect for more severe cases of ACM, where the most recovery of quality of life can potentially be gained following adequate treatment. However, the case reports included in this review reported a remarkable recovery of systolic function in 7 out of 9 patients following adequate treatment for acromegaly, indicating that (near) normalization of cardiac involvement is possible. Complete reversibility of ACM is a subject for future research in a larger cohort and falls outside the scope of this review. Studies included in this systematic review also exhibited wide heterogeneity in cardiac image acquisition and subsequent data processing, rendering reliable comparison of pooled effect size per treatment modality via meta-analysis impossible. Additionally, most studies did not report IGF-I levels as standardized IGF-I units (eg, times the upper limit of normal, or standard deviations), which limits comparability across studies.

Conclusion

This systematic review demonstrates that acromegaly-associated structural and functional myocardial changes improve with both medical and surgical treatment. Normalizing or even reducing GH/IGF-I levels may be key in the prevention of further

progression of cardiac involvement in acromegaly and adverse cardiac outcomes.

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Supplementary material

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Authors' contributions

Kevin Anthony Huynh (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Investigation [equal], Methodology [equal], Visualization [lead], Writing—original draft [lead], Writing—review & editing [lead]), Jin Al-Gully (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Investigation [equal], Methodology [equal], Writing—original draft [supporting], Writing—review & editing [supporting]), José M. Montero-Cabezas (Validation [equal], Writing—original draft [supporting]), Linda E. Scheffers (Methodology [supporting], Resources [equal], Validation [equal], Writing—original draft [supporting]), Marco Verstegen (Validation [equal], Writing—review & editing [supporting]), Nienke Biermasz (Supervision [equal], Validation [equal], Writing—original draft [supporting], Writing—review & editing [supporting]), and Eva C. Coopmans (Conceptualization [equal], Supervision [lead], Validation [equal], Writing—original draft [supporting], Writing—review & editing [supporting])

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Data availability

Data are shared upon reasonable request.

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