

Table 1. Demographic and illness severity characteristics according to duration of treatment.

	Treatment duration										Total treated	Control	P value*
	< 90 Days		90-180 Days		181-360 Days		361-720 Days		720+ Days		more than 90 days		
	(N=26)	(N=314)	(N=420)	(N=317)	(N=86)	(N=1137)	(N=672)						
Demographic characteristics													
Age (+/-SD)	44.2 (+/-10.1)	43.7 (+/-11.2)	45.6 (+/-10.1)	48.6 (+/-10.1)	48.1 (+/-9.3)	46.1 (+/-10.5)	47.1 (+/-13.4)	0.3					
Female [N (%)]	23 (88%)	257 (82%)	355 (85%)	279 (88%)	75 (87%)	966 (85%)	496 (74%)	<0.001					
Race													<0.001
Caucasian	23 (88%)	277 (88%)	383 (91%)	300 (95%)	78 (91%)	1038 (91%)	553 (82%)						
African-American	3 (12%)	18 (6%)	25 (6%)	13 (4%)	5 (6%)	61 (5%)	75 (11%)						
Asian	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (<1%)						
Hispanic	0 (0%)	17 (5%)	11 (3%)	4 (1%)	3 (3%)	35 (3%)	37 (6%)						
Other	0 (0%)	2 (<1%)	1 (<1%)	0 (0%)	0 (0%)	3 (<1%)	4 (<1%)						
Weight (+/-SD)	96.1 (+/-17.5)	98.6 (+/-21.4)	98.7 (+/-21.7)	99.1 (+/-24.4)	95.7 (+/-21.7)	98.6 (+/-22.4)	97.3 (+/-20.4)	0.5					
Body Mass Index (+/-SD)	34.5 (+/-5.3)	35.6 (+/-6.9)	35.9 (+/-7.0)	35.9 (+/-7.1)	35.2 (+/-6.2)	35.8 (+/-6.9)	34.7 (+/-6.1)	0.008					
Coexisting illness													
Hypertension	7 (27%)	63 (20%)	100 (24%)	97 (31%)	25 (29%)	285 (25%)	261 (39%)	<0.001					
Diabetes	0 (0%)	14 (4%)	29 (7%)	13 (4%)	6 (7%)	62 (5%)	85 (13%)	<0.001					
Previous myocardial infarction	0 (0%)	0 (0%)	1 (<1%)	2 (<1%)	0 (0%)	3 (<1%)	21 (3%)	<0.001					
Congestive heart failure	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	8 (1%)	0.007					
Mitral valve prolapse	0 (0%)	5 (2%)	2 (<1%)	5 (2%)	0 (0%)	12 (1%)	12 (2%)	0.7					
Smoker													0.07
Current	5 (19%)	48 (15%)	55 (13%)	37 (12%)	7 (8%)	147 (13%)	97 (14%)	0.4					
Previous	2 (8%)	78 (25%)	120 (29%)	110 (35%)	34 (40%)	342 (30%)	169 (25%)	0.03					
Hyperlipidemia	6 (23%)	73 (23%)	110 (26%)	95 (30%)	27 (31%)	305 (27%)	160 (24%)	0.2					
Depression	4 (15%)	58 (18%)	107 (25%)	62 (20%)	18 (21%)	245 (22%)	132 (20%)	0.4					
Sleep apnea	0 (0%)	11 (4%)	14 (3%)	18 (6%)	1 (1%)	44 (4%)	36 (5%)	0.2					
Rheumatoid arthritis	0 (0%)	4 (1%)	16 (4%)	12 (4%)	2 (2%)	34 (3%)	17 (3%)	0.7					
Other medications													
ACE inhibitor	0 (0%)	20 (6%)	27 (6%)	26 (8%)	10 (12%)	83 (7%)	83 (12%)	<0.001					
SSRI	3 (12%)	62 (20%)	119 (28%)	71 (22%)	22 (26%)	274 (24%)	112 (17%)	<0.001					
Months since last dose	17.6 (+/-9.2)	15.4 (+/-7.7)	14.8 (+/-9.2)	15.0 (+/-9.6)	13.6 (+/-8.5)	15.0 (+/-8.8)	-	-					

*P values for comparisons between all patients treated more than 90 days and control patients were obtained by the Fisher's exact or likelihood ratio chi-square tests for categorical variables and analysis of variance for continuous variables.

ACE - angiotensin converting enzyme SSRI - selective serotonin reuptake inhibitor

Table 2. Valve regurgitation according to duration of treatment.

[N (%)]	Treatment duration										Total treated more than 90 days	Control	P value*	
	< 90 Days		90-180 Days		181-360 Days		361-720 Days		720+ Days					
Aortic regurgitation	(N=25)		(N=313)		(N=415)		(N=315)		(N=86)		(N=1129)		N=669	<0.001
None	23	(92%)	277	(88%)	351	(85%)	234	(74%)	62	(72%)	924	(82%)	619	(93%)
Trace	1	(4%)	22	(7%)	35	(8%)	38	(12%)	9	(10%)	104	(9%)	26	(4%)
Mild	1	(4%)	10	(3%)	24	(6%)	32	(10%)	12	(14%)	78	(7%)	20	(3%)
Moderate	0	(0%)	2	(<1%)	3	(<1%)	9	(3%)	3	(3%)	17	(1%)	3	(<1%)
Moderately severe and severe	0	(0%)	2	(<1%)	2	(<1%)	2	(<1%)	0	(0%)	6	(<1%)	1	(<1%)
Mild or greater	1	(4%)	14	(4%)	29	(7%)	43	(14%)	15	(17%)	101	(9%)	24	(4%)
Mitral regurgitation	(N=25)		(N=313)		(N=412)		(N=315)		(N=86)		(N=1126)		N=668	0.008
None	15	(60%)	195	(62%)	223	(54%)	152	(48%)	43	(50%)	613	(54%)	393	(59%)
Trace	7	(28%)	75	(24%)	120	(29%)	116	(37%)	32	(37%)	343	(30%)	188	(28%)
Mild	3	(12%)	36	(12%)	57	(14%)	39	(12%)	9	(10%)	141	(13%)	77	(12%)
Moderate	0	(0%)	7	(2%)	12	(3%)	4	(1%)	0	(0%)	23	(2%)	9	(1%)
Severe	0	(0%)	0	(0%)	0	(0%)	4	(1%)	2	(2%)	6	(<1%)	1	(<1%)
Moderate or greater	0	(0%)	7	(2%)	12	(3%)	8	(3%)	2	(2%)	29	(3%)	10	(1%)
Tricuspid regurgitation	(N=24)		(N=309)		(N=407)		(N=309)		(N=84)		(N=1109)		N=662	0.8
None	13	(54%)	194	(63%)	253	(62%)	181	(59%)	51	(61%)	679	(61%)	407	(61%)
Trace	5	(21%)	70	(23%)	96	(24%)	76	(25%)	21	(25%)	263	(24%)	149	(23%)
Mild	5	(21%)	40	(13%)	52	(13%)	47	(15%)	11	(13%)	150	(14%)	93	(14%)
Moderate	1	(4%)	5	(2%)	6	(1%)	3	(<1%)	1	(1%)	15	(1%)	11	(2%)
Severe	0	(0%)	0	(0%)	0	(0%)	2	(<1%)	0	(0%)	2	(<1%)	2	(<1%)
Pulmonic regurgitation	(N=25)		(N=307)		(N=405)		(N=306)		(N=85)		(N=1103)		N=660	0.4
None	20	(80%)	242	(79%)	322	(80%)	252	(82%)	64	(75%)	880	(80%)	543	(82%)
Trace	4	(16%)	46	(15%)	69	(17%)	41	(13%)	15	(18%)	171	(16%)	82	(12%)
Mild	1	(4%)	19	(6%)	14	(3%)	12	(4%)	6	(7%)	51	(5%)	34	(5%)
Moderate	0	(0%)	0	(0%)	0	(0%)	1	(<1%)	0	(0%)	1	(<1%)	1	(<1%)
Severe	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)

*P values for comparisons between all patients treated more than 90 days and control patients were obtained by the Kruskal-Wallis test for graded regurgitation and Fisher's exact test for combined regurgitation grades.

Table 3. Valve leaflet mobility according to duration of treatment.

[N (%)]	Treatment duration										Total treated		Control	
	< 90 Days		90-180 Days		181-360 Days		361-720 Days		720+ Days		more than 90 days			
Mitral valve														
Anterior leaflet	(N=26)		(N=312)		(N=417)		(N=313)		(N=86)		(N=1128)		N=671	
Normal mobility	26	(100%)	312	(100%)	417	(100%)	310	(99%)	84	(98%)	1123	(100%)	667	(99%)
Mild restriction	0	(0%)	0	(0%)	0	(0%)	3	(<1%)	2	(2%)	5	(<1%)	4	(<1%)
Moderate restriction	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Severe restriction	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
P value*			0.2		0.2		0.6		0.09		0.7			
Posterior leaflet	(N=25)		(N=298)		(N=397)		(N=300)		(N=85)		(N=1080)		N=648	
Normal mobility	25	(100%)	287	(96%)	375	(94%)	276	(92%)	77	(91%)	1015	(94%)	618	(95%)
Mild restriction	0	(0%)	11	(4%)	21	(5%)	22	(7%)	7	(8%)	61	(6%)	27	(4%)
Moderate restriction	0	(0%)	0	(0%)	1	(<1%)	2	(<1%)	1	(1%)	4	(<1%)	3	(<1%)
Severe restriction	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
P value*			0.6		0.6		0.04		0.07		0.3			
Aortic valve	(N=26)		(N=312)		(N=414)		(N=312)		(N=86)		(N=1124)		N=670	
Normal mobility	26	(100%)	311	(100%)	411	(99%)	307	(98%)	86	(100%)	1115	(99%)	661	(99%)
Mild restriction	0	(0%)	1	(<1%)	3	(<1%)	5	(2%)	0	(0%)	9	(1%)	9	(1%)
Moderate restriction	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Severe restriction	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
P value*			0.2		0.4		0.8		0.3		0.3			

*P values for comparisons between each treatment group and control patients were obtained by the Kruskal-Wallis test.

Table 4. Echocardiographic measurements and clinical findings in treated patients with FDA criteria regurgitation compared to controls.

	FDA criteria regurgitation present		Control		P value*
	Fenfluramine-phentermine treated (N=117)		(N=672)		
Diameters [centimeters (+/-SD)]					
Left ventricular internal diameter diastolic	5.11	(+/-0.58)	5.06	(+/-0.56)	0.4
Left ventricular internal diameter systolic	3.16	(+/-0.60)	3.13	(+/-0.57)	0.4
Left atrium	3.74	(+/-0.51)	3.78	(+/-0.50)	0.5
Septal wall thickness	0.96	(+/-0.20)	0.98	(+/-0.20)	0.4
Posterior wall thickness	0.96	(+/-0.18)	0.96	(+/-0.19)	1
Aortic root	2.96	(+/-0.40)	2.98	(+/-0.43)	0.7
Estimated pulmonary artery pressure					
Mean	33.8	(+/- 6.9)	34.4	(+/-9.1)	0.7
>= 40 mmHg	3/39	(8%)	10 / 113	(9%)	1
(number positive / number evaluable)					
Leaflet thickening					
Aortic	7/117	(6%)	23/669	(3%)	0.2
Mitral	1/117	(<1%)	3/668	(<1%)	0.5
Symptoms					
Headache [N (%)]	30	(26%)	165	(25%)	0.8
Dyspnea on exertion	28	(24%)	142	(21%)	0.5
Lower extremity edema	21	(18%)	125	(19%)	1
Chest pain	10	(9%)	91	(14%)	0.2
Dizziness	10	(9%)	44	(7%)	0.4
Dyspnea at rest	8	(7%)	34	(5%)	1
Tachycardia	3	(3%)	35	(5%)	0.4
Chest Pounding	5	(4%)	22	(3%)	0.6
Syncope	0	(0%)	12	(2%)	0.2
Lightheadedness	0	(0%)	0	(0%)	-
Physical findings					
Systolic blood pressure (+/-SD)	125.6	(+/-15.7)	127.6	(+/-16.2)	0.2
Murmur	20	(17%)	44	(7%)	<0.001
Edema	3	(3%)	17	(3%)	1
Jugular venous distension	0	(0%)	0	(0%)	-
Rales	0	(0%)	1	(<1%)	1
Wheezing	0	(0%)	7	(1%)	0.6

*P values for comparisons between groups were obtained by Fisher's exact or likelihood chi-square tests for categorical variables and analysis of variance for continuous variables.

FDA criteria regurgitation - Food and Drug Administration criteria of mild or greater aortic valve or moderate or greater mitral valve insufficiency.

Table 5. Symptoms and physical findings according to duration of treatment.

[N (%)]	Treatment duration										Total treated		Control	P value*	
	< 90 Days		90-180 Days		181-360 Days		361-720 Days		720+ Days		more than 90 days				
	(N=26)	(N=314)	(N=420)	(N=317)	(N=86)	(N=1137)	N=672								
Symptoms															
Headache	6	(23%)	67	(21%)	120	(29%)	96	(30%)	32	(37%)	315	(28%)	165	(25%)	0.2
Dyspnea on exertion	4	(15%)	59	(19%)	104	(25%)	100	(32%)	29	(34%)	292	(26%)	142	(21%)	0.03
Lower extremity edema	7	(27%)	46	15%)	81	(19%)	60	(19%)	26	(30%)	213	(19%)	125	(19%)	1
Chest pain	3	(12%)	32	(10%)	45	(11%)	30	(9%)	8	(9%)	115	(10%)	91	(14%)	0.03
Dizziness	1	(4%)	16	(5%)	26	(6%)	18	(6%)	12	(14%)	72	(6%)	44	(7%)	0.8
Dyspnea at rest	0	(0%)	13	(4%)	24	(6%)	11	(3%)	8	(9%)	56	(5%)	34	(5%)	0.9
Tachycardia	3	(12%)	10	(3%)	18	(4%)	14	(4%)	3	(3%)	45	(4%)	35	(5%)	0.3
Chest Pounding	0	(0%)	8	(3%)	17	(4%)	8	(3%)	5	(6%)	38	(3%)	22	(3%)	1
Syncope	1	(4%)	5	(2%)	10	(2%)	3	(<1%)	2	(2%)	20	(2%)	12	(2%)	1
Lightheadedness	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	-
Physical findings															
Systolic blood pressure (+/-SD)	125.8	(+/-14.3)	125.0	(+/-14.2)	126.3	(+/-15.3)	129.9	(+/-18.3)	124.3	(+/-16.5)	126.8	(+/-16.1)	127.6	(+/-16.2)	0.2
Diastolic blood pressure (+/-SD)	79.8	(+/-11.0)	79.5	(+/-9.1)	80.5	(+/-9.3)	80.1	(+/-9.9)	78.9	(+/-9.3)	80.0	(+/-9.4)	79.6	(+/-9.8)	0.7
Pulse (+/-SD)	75.7	(+/-10.9)	75.5	(+/-10.0)	75.4	(+/-8.9)	74.8	(+/-8.9)	76.2	(+/-8.5)	75.3	(+/-9.2)	74.3	(+/-8.9)	0.02
Murmur	3	(12%)	17	(5%)	22	(5%)	35	11%)	8	(9%)	82	(7%)	44	(7%)	0.6
Edema	0	(0%)	2	(<1%)	9	(2%)	10	(3%)	2	(2%)	23	(2%)	17	(3%)	0.5
Jugular venous distension	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	-
Rales	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(<1%)	0.4
Wheezing	0	(0%)	1	(<1%)	1	(<1%)	3	(<1%)	2	(2%)	7	(<1%)	7	(1%)	0.4

*P values for comparisons between all patients treated more than 90 days and control patients were obtained by the Fisher's exact or likelihood ratio chi-square tests for categorical variables and analysis of variance for continuous variables.

Appendix 2 Multivariate logistic regression analyses

Aortic regurgitation of mild or greater severity

Variable	Parameter estimate	Wald chi-square	P	Odds ratio	(95% confidence limits)
Treatment 90-180 days	0.42	1.5	0.3	1.53	(0.77, 3.03)
Treatment 181-360 days	0.88	9.3	0.003	2.42	(1.37, 4.26)
Treatment 361-720 days	1.53	32.3	0.0001	4.62	(2.73, 7.82)
Treatment 720+ days	1.83	25.9	0.0001	6.21	(3.08, 12.56)
Age	0.04	19.4	0.0001	1.04	
Body mass index	-0.06	10.3	0.002	0.95	
Intercept	-3.39	17.6	0.0001		

c index = 0.73

Hosmer-Lemeshow statistic P=0.46

Mitral regurgitation of moderate or greater severity

Variable	Parameter estimate	Wald chi-square	P	Odds ratio	(95% confidence intervals)
Treatment 90-180 days	0.57	1.3	0.2	1.77	(0.66, 4.77)
Treatment 181-360 days	0.79	3.3	0.08	2.21	(0.93, 5.22)
Treatment 361-720 days	0.55	1.3	0.3	1.73	(0.67, 4.44)
Treatment 720+ days	0.48	0.4	0.6	1.61	(0.35, 7.50)
Age	0.04	6.2	0.02	1.04	
Intercept	-6.05	49.8	0.0001		

c index = 0.64

Hosmer-Lemeshow statistic P=0.15