SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Methodological details on the multicentre Italian Society of Interventional Cardiology (GIse) registry Of Transcatheter treatment of mitral valve regurgitaTiOn (GIOTTO) have been previously reported in detail, including study design, ethical approval and online registration.(24) Specifically, data collection was based on web electronic case report forms (eCRF), periodically crosschecked for accuracy.

Transthoracic and transesophageal echocardiography evaluations were performed at study sites before the procedure. Transesophageal echocardiography was assessed during the procedure and transthoracic echocardiography at discharge and, for the available patients, during the follow-up. All echocardiography parameters were evaluated according to the American Society of Echocardiography recommendations, and the same applied to mitral regurgitation severity, which was graded as follows: 1+ (mild), 2+ (moderate), 3+ (moderate-to-severe) and 4+ (severe).(25)

Clinical follow-up data were entered into eCRF by local investigators after being obtained by inpatient or outpatient clinical visits and/or telephone calls scheduled at 30 days, 1 year, and yearly.(24)

Outcomes were adjudicated according to the Mitral Valve Academic Research Consortium by local investigators, and then entered into the dedicated eCRF system.(18) Specifically, device success for transcatheter mitral valve repair was defined as: absence of procedural mortality or stroke, proper placement and positioning of the device, freedom from unplanned surgical or interventional procedures related to the device or access procedure, and continued intended safety and performance of the device, including reduction of mitral regurgitation to either optimal/acceptable levels without significant mitral stenosis, no evidence of structural or functional failure, no specific device-related technical failure issues and complications, no greater than mild paravalvular mitral regurgitation, and no associated hemolysis.

Procedural success for transcatheter mitral valve repair was defined as: device success in the absence of major device or procedure related serious adverse events, including death, stroke, life-threatening bleeding, major vascular complication, major cardiac structural complications, stage 2 or 3 acute kidney injury (includes new dialysis), myocardial infarction or coronary ischemia requiring percutaneous or surgical revascularization, severe hypotension, heart failure, or respiratory failure requiring intravenous pressors or invasive or mechanical heart failure treatments, valve-related dysfunction, migration, thrombosis, or other complication requiring surgery or repeat intervention.

Supplemental Results

The median time between prior MitraClip implantation and subsequent MitraClip redo was 34 months, with a minimum of months and a maximum of 81 months.

An ancillary analysis focusing on the long-term impact of post-procedural mitral gradients suggested no significant role on most outcomes, except for death or rehospitalization, even if the risk of multiplicity cannot be disregarded, also given that this finding was significant only when considering this variable as a continuous one (Table S3).

Table S1. Imaging at echocardiography and invasive coronary angiography, and electrocardiographic features.

Feature	Naïve	Prior MitraClip	Prior mitral surgery	Overall P	Subgroup P*
Patients	2169	29	40	-	-
LV end-diastolic diameter (mm)	59.1±10.8	64.0±9.6	56.5±9.7	0.018	0.003
LV end-systolic diameter (mm)	44.2±13.1	52.0±9.9	44.7±14.2	0.013	0.048
LV end-diastolic volume (mL)	157±69	188±85	141±53	0.025	0.010
LV end-systolic volume (mL)	95±60	128±75	77±46	0.003	0.001
LV ejection fraction (%)	42.5±14.8	33.2±12.6	49.3±13.7	<0.001	<0.001
Mean mitral gradient (mm Hg)	2.1±0.9	2.6±0.9	3.4±2.2	<0.001	0.434
Severe mitral regurgitation	1696 (78.2%)	17 (58.6%)	33 (82.5%)	0.041	0.054
Tethering				0.061	0.706
No	1410 (65.0%)	24 (82.8%)	33 (82.5%)		
Symmetric	479 (22.1%)	4 (13.8%)	4 (10.0%)		
Asymmetric	280 (12.9%)	1 (3.5%)	3 (7.5%)		
Leaflet prolapse	610 (28.1%)	3 (10.3%)	24 (60.0%)	<0.001	<0.001
Flail leaflet	441 (20.3%)	2 (6.9%)	14 (35.0%)	0.015	0.008
Severe calcification	105 (4.8%)	1 (3.5%)	1 (2.5%)	1	1
Tricuspid regurgitation				0.018	0.027
None	106 (4.9%)	1 (3.5%)	5 (12.5%)		
Mild	823 (37.9%)	5 (17.2%)	16 (40.0%)		
Moderate	953 (43.9%)	18 (62.1%)	11 (27.5%)		
Severe	287 (13.2%)	5 (17.2%)	8 (20.0%)		
Systolic pulmonary artery pressure (mm Hg)	47±14	52±16	43±15	0.080	0.042
Coronary angiography	956 (44.1%)	10 (34.5%)	23 (57.5%)	0.138	0.087
Coronary artery disease type				0.587	0.310
None	602 (63.0%)	5 (50.0%)	16 (69.6%)		
Single vessel disease	155 (16.2%)	3 (30.0%)	4 (17.4%)		
Two vessel disease	95 (9.9%)	2 (20.0%)	1 (4.4%)		
Three vessel disease	59 (6.2%)	0	0		
Left main disease	45 (4.7%)	0	2 (8.7%)		
Any ECG abnormality	589 (27.2%)	12 (41.4%)	15 (37.5%)	0.075	0.806
Type II AV block	4 (0.2%)	0	0	1	1
Type III AV block	7 (0.3%)	0	0	1	1
Right bundle branch block	54 (2.5%)	1 (3.5%)	1 (2.5%)	0.651	1
Left bundle branch block	79 (3.6%)	3 (10.3%)	0	0.083	0.070
Atrial fibrillation	462 (21.3%)	5 (17.2%)	15 (37.5%)	0.054	0.106

*comparing patients with prior MitraClip implantation vs those with prior mitral surgery;
AV=atrioventricular

Table S2. Medical therapy at discharge.

Feature	Naïve	Prior MitraClip	Prior mitral surgery	Overall P	Subgroup P*
Patients	2108	28	40	-	-
Angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker	641 (30.6%)	6 (20.7%)	5 (12.5%)	0.020	0.507
Calcium channel antagonist	178 (8.5%)	2 (6.9%)	1 (2.5%)	0.499	0.568
Beta-blocker	1589 (75.7%)	23 (79.3%)	32 (80.0%)	0.815	1
Ivabradine	104 (5.0%)	1 (3.5%)	2 (5.0%)	1	1
Furosemide	1957 (93.3%)	27 (93.1%)	37 (92.5%)	0.859	1
Furosemide daily dose (mg)	82.3±83.7	110.2±80.9	61.3±32.4	0.070	0.002
Potassium-sparing diuretic	1171 (56.1%)	20 (69.0%)	31 (77.5%)	0.009	0.579
Aspirin	1217 (58.1%)	14 (48.3%)	26 (65.0%)	0.387	0.218
Thienopyridine	941 (45.0%)	16 (55.2%)	19 (47.5%)	0.525	0.628
Anti-vitamin K agent	521 (24.9%)	9 (31.0%)	11 (27.5%)	0.621	0.793
Novel oral anticoagulant	521 (24.9%)	6 (20.7%)	11 (27.5%)	0.838	0.581
Inotropic agent	18 (0.9%)	1 (3.5%)	0	0.264	0.420

Table S3. Association between clinical outcomes and mean mitral gradient at discharge.

Outcome	Hazard ratio		P
	Point estimate	95% confidence interval	
Gradient as continuous variable (mm Hg)			
Death	1.03	0.99-1.07	0.099
Cardiac death	1.02	0.96-1.07	0.588
Rehospitalization	1.01	0.96-1.07	0.600
Rehospitalization for heart failure	1.01	0.95-1.07	0.838
Death or rehospitalization	1.03	1.00-1.06	0.041
Cardiac death or rehospitalization for heart failure	1.02	0.98-1.06	0.301
Heart failure	1.02	0.98-1.08	0.330
Gradient as dichotomous variable (>5 vs ≤5 mm Hg)			
Death	1.20	0.94-1.59	0.139
Cardiac death	0.99	0.66-1.47	0.972
Rehospitalization	1.00	0.69-1.45	0.997
Rehospitalization for heart failure	1.02	0.69-1.53	0.907
Heart failure	1.05	0.73-1.52	0.789
Death or rehospitalization	1.24	0.99-1.56	0.067
Cardiac death or rehospitalization for heart failure	1.07	0.80-1.43	0.655