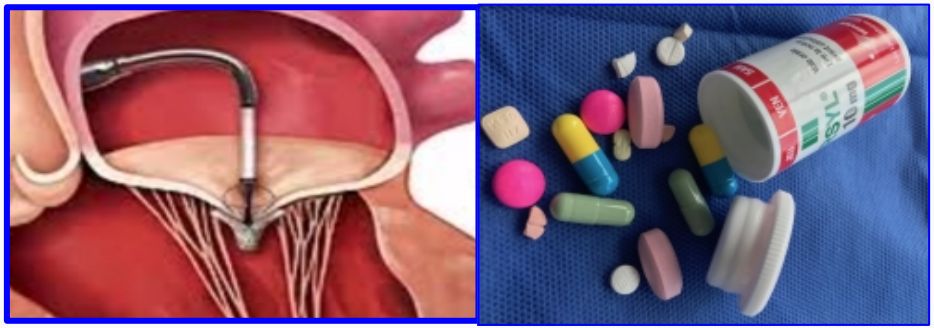
Percutaneous Repair with the MitraClip Device for Severe Secondary Mitral Regurgitation



Pr Jean François OBADIA - LYON

on behalf of the MITRA-FR Investigators

ESC Congress
Munich 2018

Declaration of interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company (abbott, Edwards, Medtronic, Landanger, Delacroix Chevalier, Novartis)
- Research contracts (Abbott, Neochord)
- Consulting/Royalties/Owner/ Stockholder of a healthcare company (abbott, Edwards, Medtronic, Landanger, Delacroix Chevalier, Novartis)
- Research contracts (Abbott, Neochord)

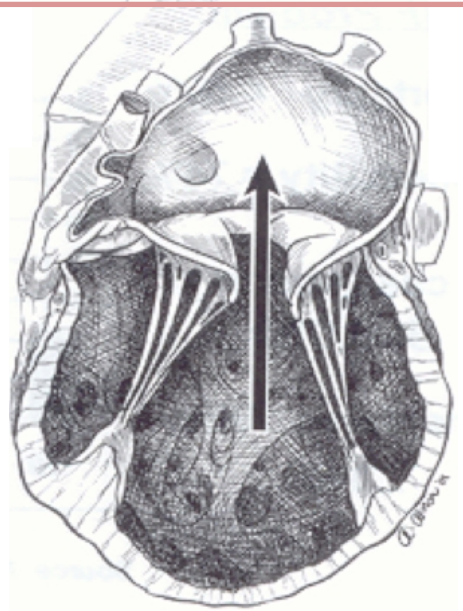
Declaration of Interest

Research grant *:* **Abbott, Neochord**

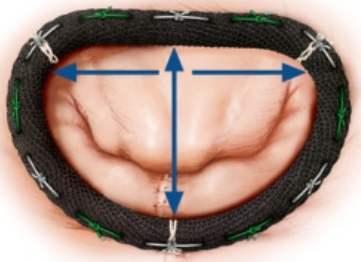
Consulting fee : **Delacroix-Chevalier, Edwards, Landanger, Medtronic, Novartis, SJM, Servier**

Background

Secondary / Functional



Treatment



Recommendations

2017 ESC/EACTS Guidelines

.....a percutaneous edge-to-edge procedure may be considered.....

-Grigioni et al Circulation 2001

-Baumgartner et al. Europ Heart J 2017

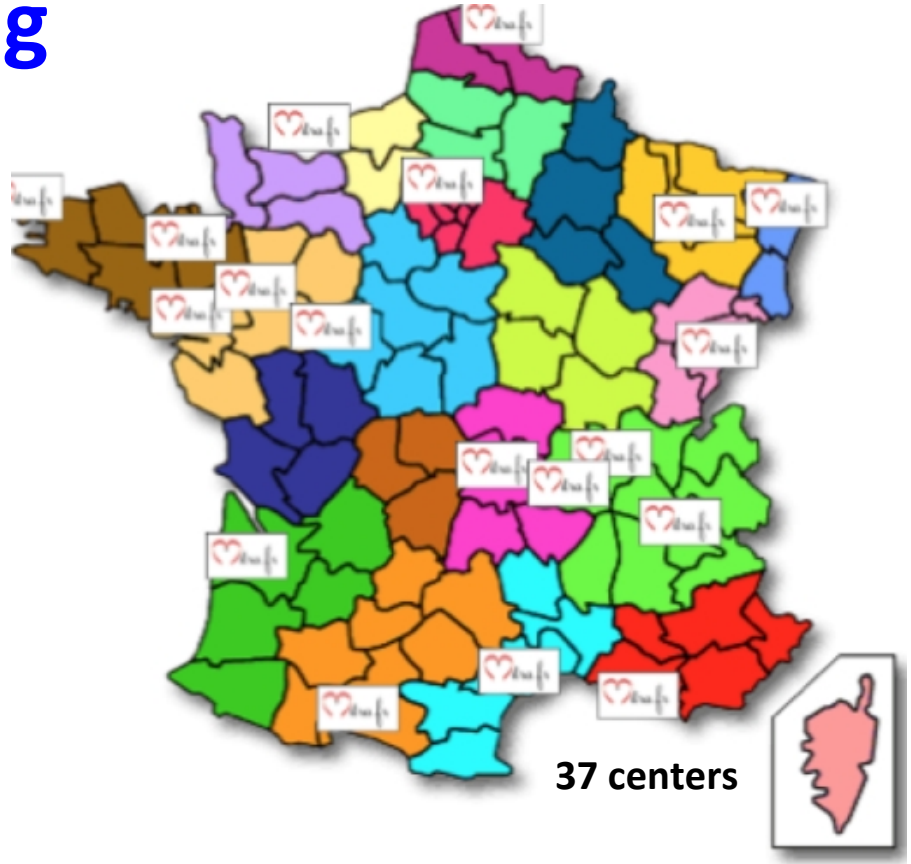
Study funding

- **<u>Study Sponsor</u>:** Hospices Civils de Lyon

Academic Study supported by a French Research Program grant from ministry of Health "**PHRC**"

* **<u>Abbott Vascular involvement</u> :**

- Proctoring of the teams
- Financing 84% of the clips



Study Design*

Objective → to evaluate the clinical efficacy of percutaneous mitral valve repair in addition to medical treatment in patients with heart failure and severe functional/secondary mitral regurgitation versus medical treatment alone.

Primary Endpoint "Composite" → All-Cause Deaths or Unplanned rehospitalization for Heart failure at 12 months

* *Obadia et al. Eurointervention 2015;10:1354-1360*

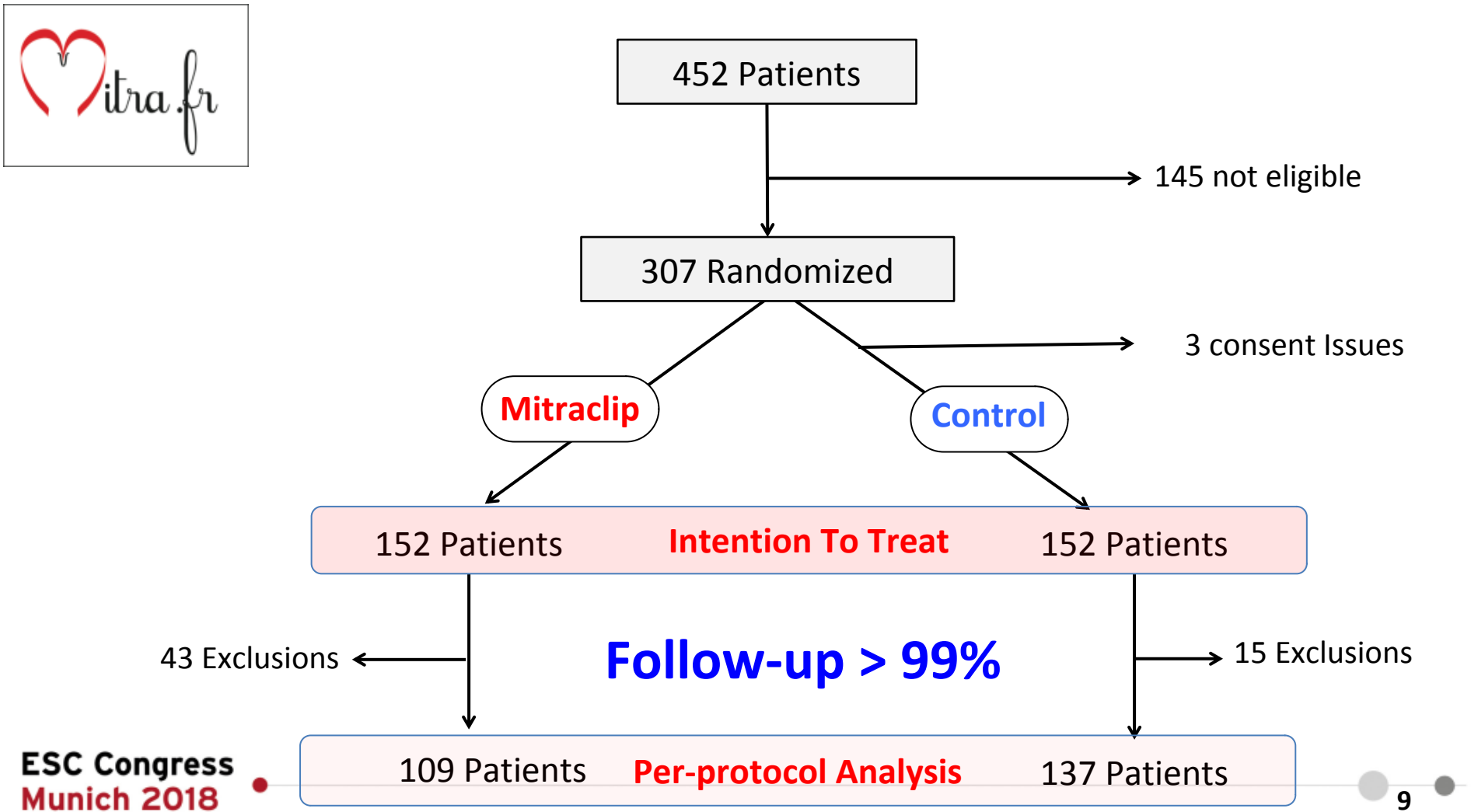
Sample Size Calculation

- Primary End Point hypothesis at 12 months :
  - Control group ➔ 50% “Death or unplanned Re-hospitalization”
  - Mitraclip group ➔ 33% “Death or unplanned Re-hospitalization”
- Superiority design :
  - Bilateral Risk alpha 0.05 / power 80%
  - 10 % lost to follow-up

288 ➔ 144 x 2 per arm

Inclusion Criteria

- **Symptomatic** despite Optimal Treatment (NYHA ≥II).
- At least **one hospitalization** for HF within 12 months preceding randomization
- Severe Secondary MR ➔ **ERO > 20 mm²** or R.vol>30 mL/beat
- **15% < EF < 40%**
- Not eligible for surgery "Heart Team"
- **Centralized echocardiographic Corelab**


452 Patients
145 not eligible
307 Randomized
3 consent Issues
Mitraclip
Control
152 Patients
Intention To Treat
152 Patients
43 Exclusions
Follow-up > 99%
15 Exclusions
109 Patients
Per-protocol Analysis
137 Patients

Baseline characteristics

Characteristics	Percutaneous Repair Group (n=152)	Optimal Medical Treatment Group (n=152)	P value
Age year mean (±SD)	70.1 ± 10.1	70.6 ± 9.9	0.69
>75 year n (%)	51 (33.6)	59 (38.8%)	0.40
Males n - (%)	120 (78.9)	107 (70.4%)	0.11
Ischemic Cardiomyopathy n - (%)	95 (62.5)	85 (56.3%)	0.29
NYHA Class II n - (%)	56 (36.8)	44 (28.9%)	
NYHA Class III n - (%)	82 (53.9)	96 (63.2%)	0.27
NYHA Class IV n - (%)	14 (9.2)	12 (7.9%)	
LVEF mean (±SD)	33.3 ± 6.5	32.9 ± 6.7	0.79
Effect regurg. Orif. area - mm^2 mean (±SD)	31 ± 10	31 ± 11	0.42

60%

2/3

EF=33%

$S=31mm^2$

Baseline characteristics

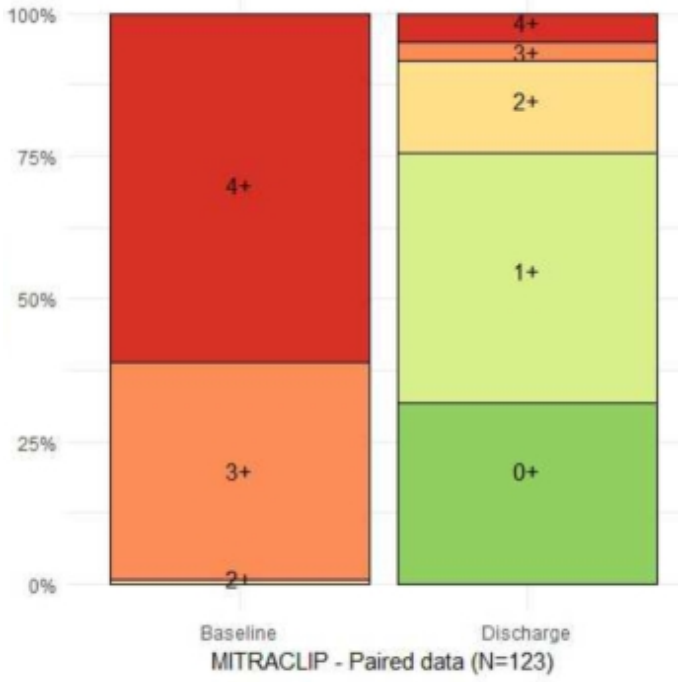
Characteristics	Percutaneous Repair Group	Optimal Medical Treatment Group	P value
NTproBNP - ng/L median [IQR]	3407 [1948; 6790]	3292 [1937; 6343]	0.97
Implantable cardioverter-defibrillator	90 (59.2%)	82 (53.9%)	0.42
Diuretics	151 (99.3%)	149 (98.0%)	0.62
Beta-blockers	134 (88.2%)	138 (90.8%)	0.57
ACE- inhibitor / ARB	111 (73.0%)	113 (74.3%)	0.55
Mineralocorticoid Receptor Antagonist	86 (56.6%)	80 (53.0%)	0.56
ARB and Neprilysin Inhibitor	14 (10.0%)	17 (12.1%)	0.70
Systolic Blood Pressure mmHg mean (±SD)	109 ± 16	108 ± 18	0.78

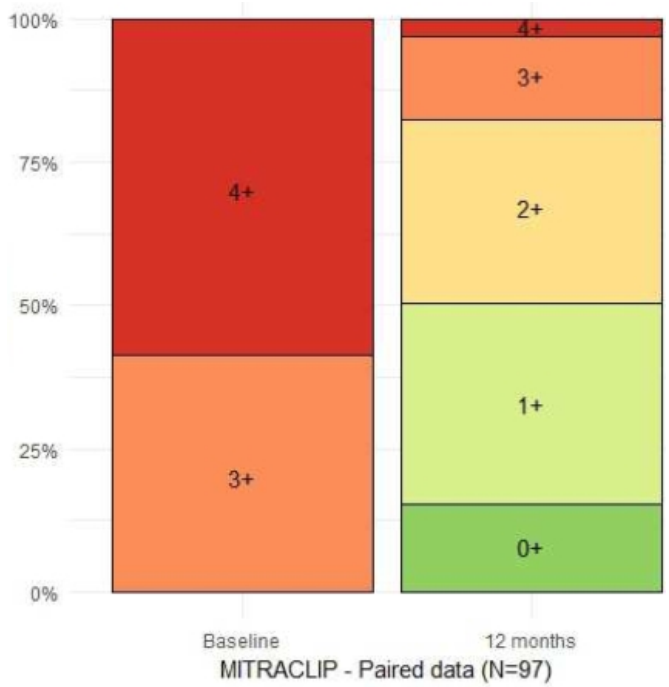
Prespecified Secondary Endpoints

* Safety	Peri procedural complications
Urgent conversion to heart surgery	0
Peri-procedural Mortality (at 3 days)	0
Vascular complication requiring surgery / Hemorrhage transfusion	5 (3.5%)
Cardiac embolism (Gas embolism / Stroke)	2 (1.4%)
Tamponade	2 (1.4%)
* Efficacy Technical Implantation Success MVARC	138 (96%) - 1 Clip ➔ 46% - 2 Clips ➔ 45% - 3+ Clips ➔ 9%

Prespecified Secondary Endpoints

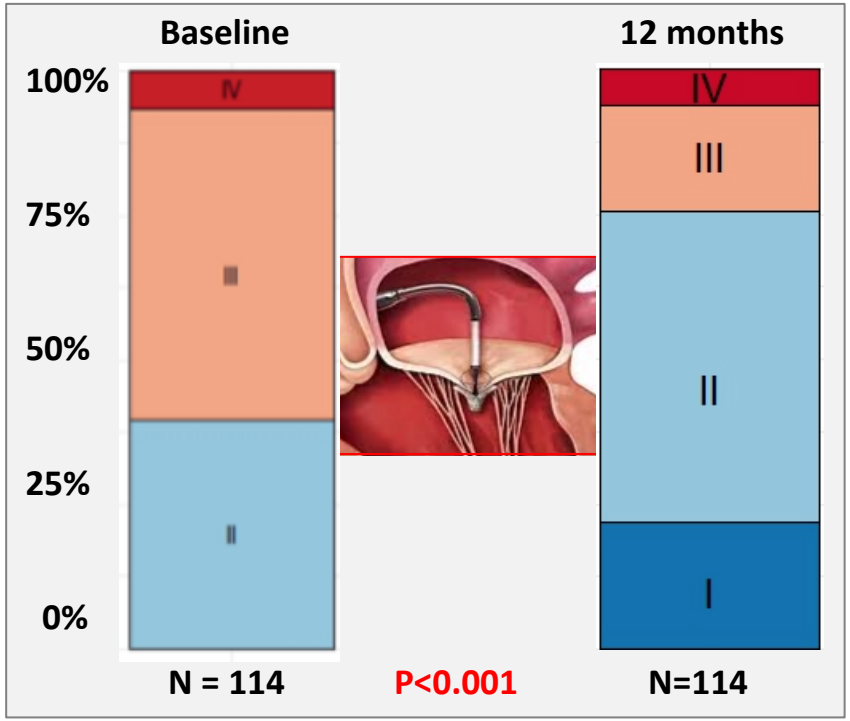
MR Grade evolution Corelab





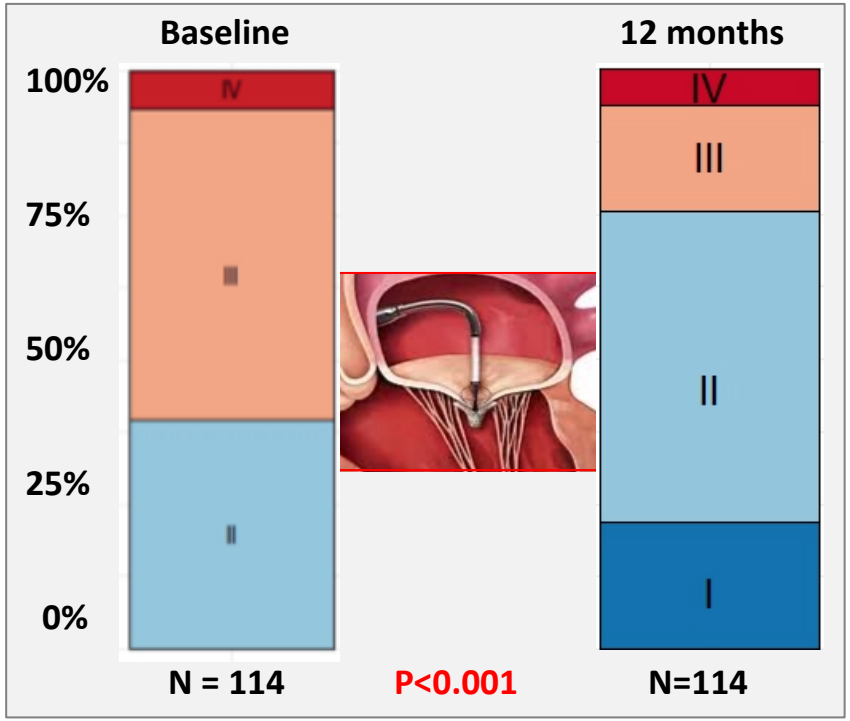
Prespecified Secondary Endpoints

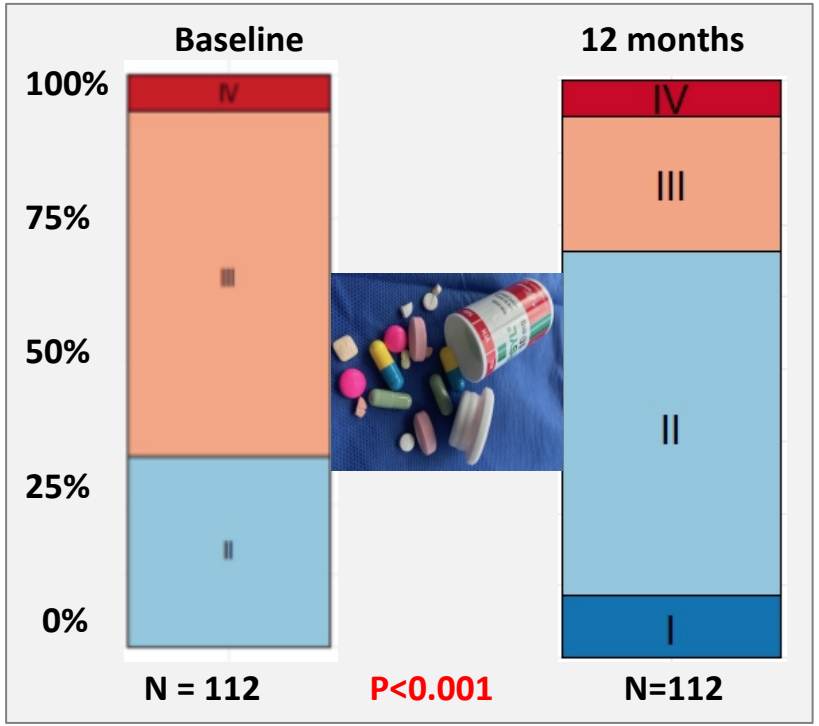
NYHA evolution (*123 paired data)*



Prespecified Secondary Endpoints

NYHA evolution (*paired data)*



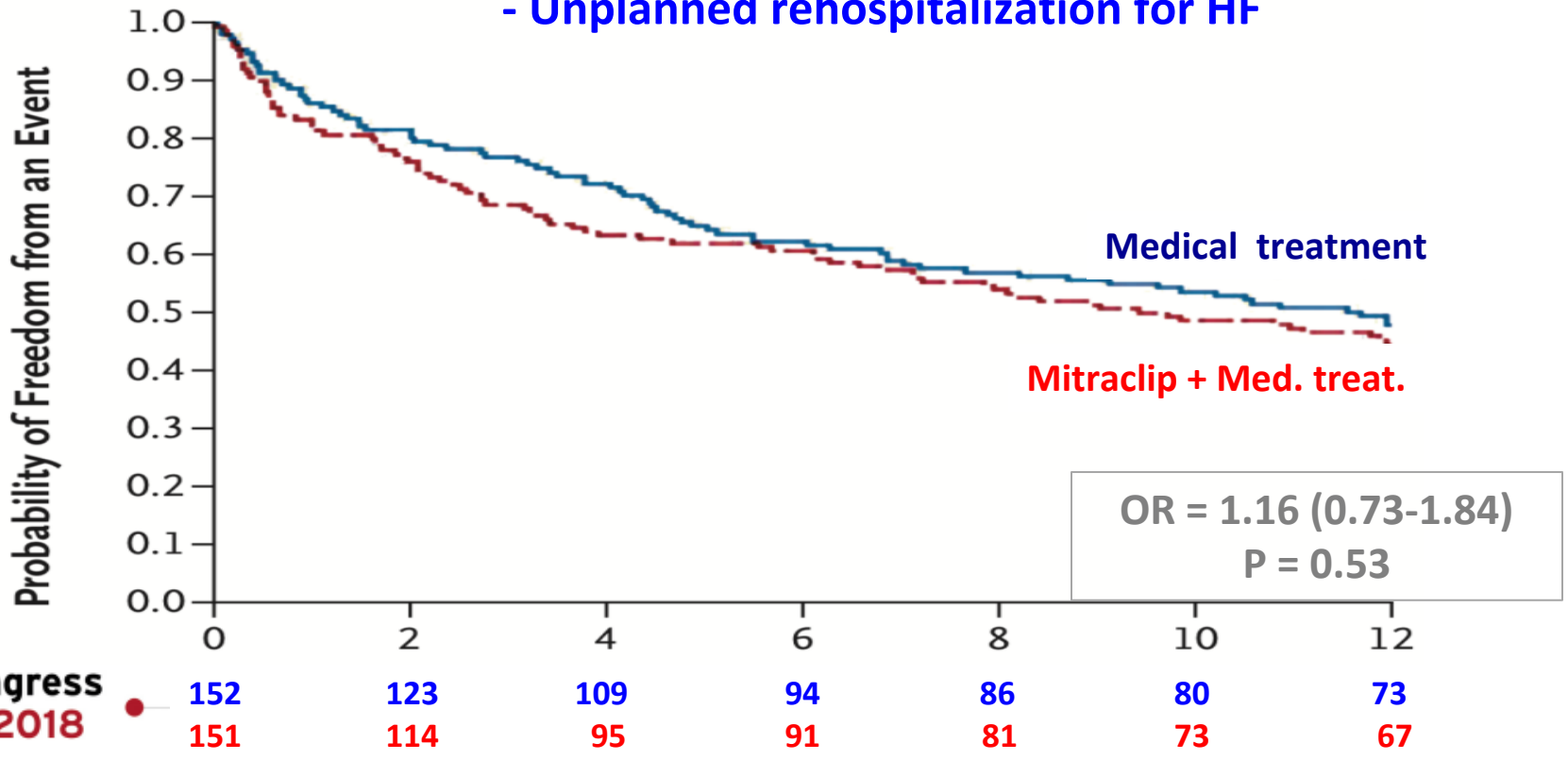


P = NS

Primary Endpoint

Primary composite endpoint *(99% follow-up)*

- All-Cause Death
- Unplanned rehospitalization for HF



ESC Congress
Munich 2018

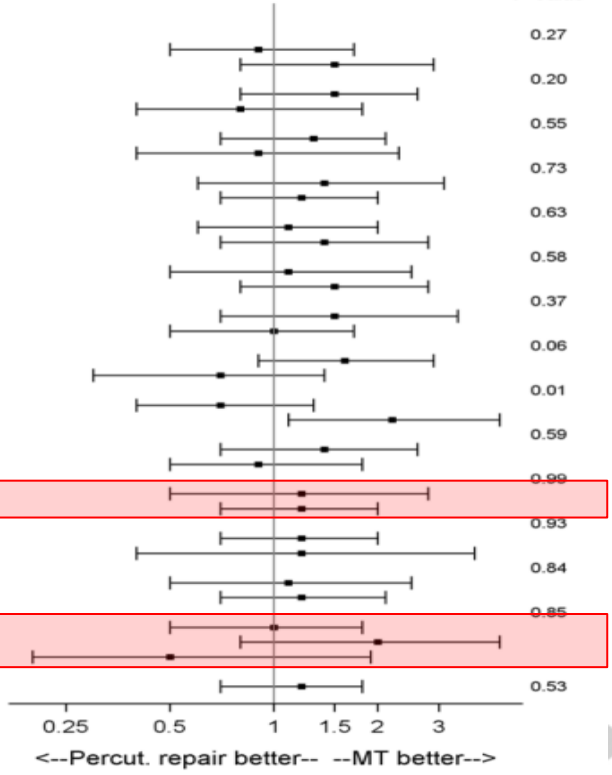
Intention to treat	Percutaneous Repair (n=152)	Medical treatment (n=152)	P value
All-cause death + unplanned hospitalization for heart failure	83 (**54.6%**)	78 (**51.3%**)	**0.53**
All-Cause Death	37 (24.3%)	34 (22.4%)	0.66
Unplanned rehospitalization for heart failure	74 (48.7%)	72 (47.4%)	0.47

Per-protocol analysis	Percutaneous Repair Group (n=109)	Medical Treatment (n=137)	P value
All-cause death and unplanned hospitalization for heart failure	62 (**56.9%**)	72 (**52.6%**)	0.51
All-Cause Death	26 (23.9%)	32 (23.4%)	0.83
Unplanned rehospitalization for heart failure	56 (51.4%)	67 (48.9%)	0.34

Prespecified Secondary Endpoints

Subgroup Analysis

Subgroup	Percut. repair Events/N (%)		Medical treatment Events/N (%)		OR (95% CI)	P Value*
CENTRE SIZE						0.27
N <= 15 Randomized patients	33/73	(45.2)	35/73	(47.9)	0.90 (0.50, 1.70)	
N > 15 Randomized patients	50/77	(64.9)	43/78	(55.1)	1.50 (0.80, 2.90)	
AGE						0.20
<= 75 Yr	52/100	(52.0)	39/93	(41.9)	1.50 (0.80, 2.60)	
> 75 Yr	31/50	(62.0)	39/58	(67.2)	0.80 (0.40, 1.80)	
GENDER						0.55
Male	67/120	(55.8)	53/106	(50.0)	1.30 (0.70, 2.10)	
Female	16/30	(53.3)	25/45	(55.6)	0.90 (0.40, 2.30)	
NYHA						0.73
Class II	26/56	(46.4)	17/44	(38.6)	1.40 (0.60, 3.10)	
Class III/IV	57/94	(60.6)	61/107	(57.0)	1.20 (0.70, 2.00)	
ISCHEMIC CARDIOMYOPATHY						0.63
Yes	49/94	(52.1)	42/84	(50.0)	1.10 (0.60, 2.00)	
No	34/56	(60.7)	35/66	(53.0)	1.40 (0.70, 2.80)	
PULMONARY ARTERY PRESSURE						0.58
< 50 mmHg	23/53	(43.4)	18/44	(40.9)	1.10 (0.50, 2.50)	
≥ 50 mmHg	49/73	(67.1)	51/88	(58.0)	1.50 (0.80, 2.80)	
ATRIAL FIBRILLATION						0.37
Yes	30/49	(61.2)	24/47	(51.1)	1.50 (0.70, 3.40)	
No	46/91	(50.5)	51/99	(51.5)	1.00 (0.50, 1.70)	
PREVIOUS HOSPIT FOR CHF						0.06
< 2	53/95	(55.8)	38/87	(43.7)	1.60 (0.90, 2.90)	
≥ 2	30/55	(54.5)	40/62	(64.5)	0.70 (0.30, 1.40)	
CREATININE						0.01
< 1 5 mg/dl	31/75	(41.3)	43/85	(50.6)	0.70 (0.40, 1.30)	
≥ 1 5 mg/dl	51/72	(70.8)	34/65	(52.3)	2.20 (1.10, 4.50)	
HEMOGLOBINE						0.59
< Median	43/75	(57.3)	33/65	(50.8)	1.40 (0.70, 2.60)	
≥ Median	38/72	(52.8)	42/80	(52.5)	0.90 (0.50, 1.80)	
LVEF						0.99
< 30%	21/35	(60.0)	27/48	(56.3)	1.20 (0.50, 2.80)	
≥ 30%	62/115	(53.9)	51/102	(50.0)	1.20 (0.70, 2.00)	
TRICUSPID REGURGITATION						0.93
Mild	60/110	(54.5)	60/118	(50.8)	1.20 (0.70, 2.00)	
Moderate/Severe	19/29	(65.5)	14/23	(60.9)	1.20 (0.40, 3.80)	
LV TELEDIASTOLIC DIAMETER						0.84
< 65 mm	21/43	(48.8)	21/45	(46.7)	1.10 (0.50, 2.50)	
≥ 65 mm	62/107	(57.9)	56/105	(53.3)	1.20 (0.70, 2.10)	
MITRAL REGURGITANT ORIFICE						0.85
< 30 mm2	37/77	(48.1)	39/80	(48.8)	1.00 (0.50, 1.80)	
30-40 mm2	28/44	(63.6)	24/51	(47.1)	2.00 (0.80, 4.50)	
> 40 mm2	18/29	(62.1)	15/20	(75.0)	0.50 (0.20, 1.90)	
OVERALL	83/150	(55.3)	78/151	(51.7)	1.20 (0.70, 1.80)	0.53



Conclusion

Mitra.fr is the first Prospective Randomized Study assessing the correction of Secondary Mitral Regurgitation among heart failure patients

1) *Is percutaneous correction of 2MR with Mitraclip Safe and effective ?* *YES*

2) *Does correction of 2MR change the prognosis ?* *NO*

Consistent results of Mitra.fr suggests that the cause of the poor clinical outcome is more the underlying cardiomyopathy than the MR which is probably mainly a marker of severity

The limit of our study concerns the possibly too small subgroups in our secondary analysis so that more randomized studies are necessary to define possible indications, underestimated by Mitra.fr

Mitra.fr

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation

J.-F. Obadia, D. Messika-Zeitoun, G. Leurent, B. Iung, G. Bonnet, N. Piriou, T. Lefèvre, C. Piot, F. Rouleau, D. Carrié, M. Nejjari, P. Ohlmann, F. Leclercq, C. Saint Etienne, E. Teiger, L. Leroux, N. Karam, N. Michel, M. Gilard, E. Donal, J.-N. Trochu, B. Cormier, X. Armoiry, F. Boutitie, D. Maucort-Boulch, C. Barnel, G. Samson, P. Guerin, A. Vahanian, and N. Mewton, for the MITRA-FR Investigators.

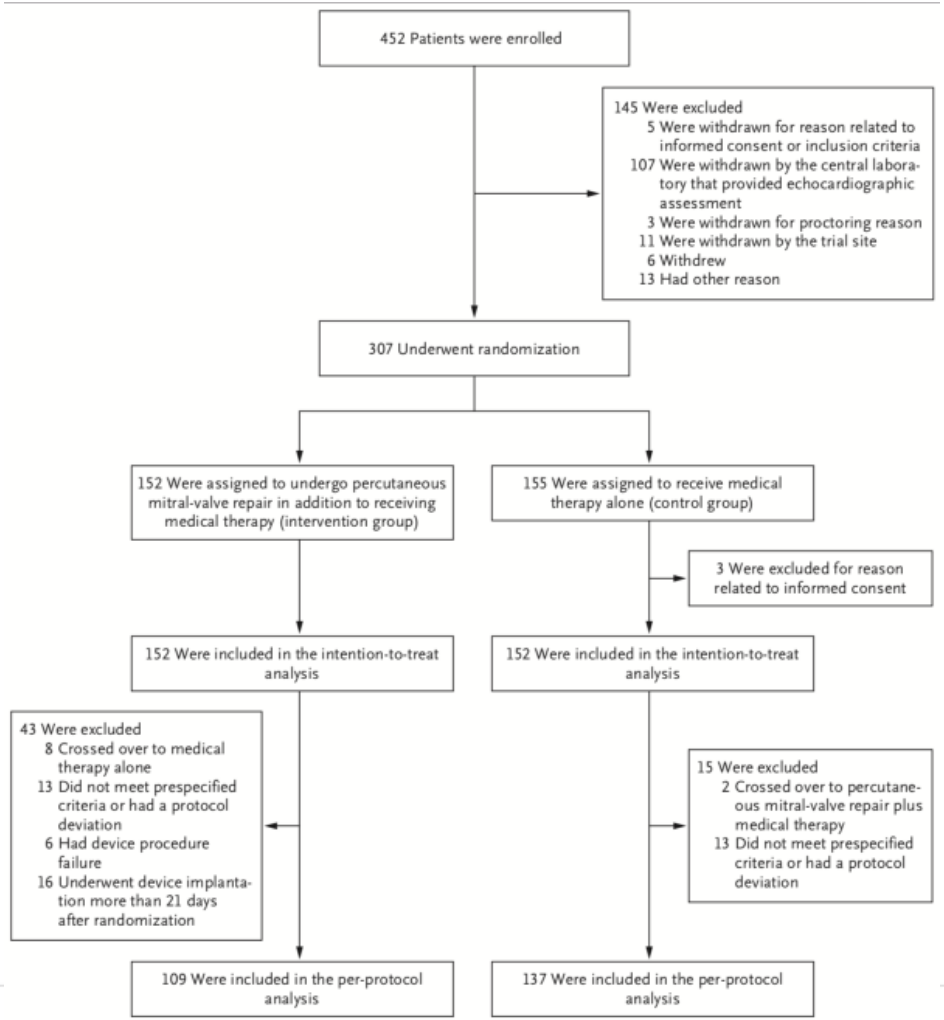
https://www.nejm.org

Extra slides

Secondary Echocardiographic End Points at 12 months

	Percutaneous Repair Group (n=152)			Optimal Medical Treatment Group (n=152)			P value for comparison between study groups
Change from baseline in echocardiographic measures	N	Value	P value between Baseline and 12 Mo	N	Value	P value between Baseline and 12 Mo	
Effective regurgitant orifice area - mm²	60	**-15** [-23.5 ; -8]	<0.0001	71	**-4** [-11 ; 5]	0.03	<0.0001
End-systolic diameter - mm	89	2 [-2 ; 7]	0.002	81	0 [-3 ; 4]	0.92	0.06
Ejection fraction - %	86	-3 [-8 ; 4]	0.14	76	2 [-4 ; 8]	0.02	0.004
Pulmonary artery systolic pressure - mmHg	64	-6.5 [-18 ; 4.5]	0.001	59	-3 [-17 ; 3]	0.007	0.81
6-minute walk variation - m	73	25 [-40 ; 71]	0.08	57	19 [-27 ; 75]	0.06	0.82

Mitra.fr


452 Patients were enrolled
145 Were excluded
5 Were withdrawn for reason related to informed consent or inclusion criteria
107 Were withdrawn by the central laboratory that provided echocardiographic assessment
3 Were withdrawn for proctoring reason
11 Were withdrawn by the trial site
6 Withdrew
13 Had other reason
307 Underwent randomization
152 Were assigned to undergo percutaneous mitral-valve repair in addition to receiving medical therapy (intervention group)
155 Were assigned to receive medical therapy alone (control group)
3 Were excluded for reason related to informed consent
152 Were included in the intention-to-treat analysis
152 Were included in the intention-to-treat analysis
43 Were excluded
8 Crossed over to medical therapy alone
13 Did not meet prespecified criteria or had a protocol deviation
6 Had device procedure failure
16 Underwent device implantation more than 21 days after randomization
15 Were excluded
2 Crossed over to percutaneous mitral-valve repair plus medical therapy
13 Did not meet prespecified criteria or had a protocol deviation
109 Were included in the per-protocol analysis
137 Were included in the per-protocol analysis

	Everest II N=279	MITRA-FR N=304	Access Europ N=567	Sentinel Pilot N=628	TRAMI N=740
Secondary MR	27%	100%	77%	72%	71%
Mean Age	67y	70y	74y	74y	76y
Mean EF	60 %	33 %	NA	43%	NA
Procedural success	77%	94%	91%	95%	97%
30 days Mortality	1%	2.3 %	3.4%	NA	4.5%
1 year Follow-up	73%	> 99%	NA	NA	NA
1y NYHA I/II	98%	72%	71%	74%	63%
1y MR Grade III/IV	18%	17 %	21.1%	NA	NA
1 y Mortality	6.1 %	24.3 %	17.3%	15.3%	20.3%
1 y Hospit for HF	NA	48.7 %	NA	NA	34%

37 French centres

CHU Caen

CHU Rouen

CHU Brest

CHU Rennes

CHU Angers

CHU Nantes

Tours (CHU, Saint Gatien)

CHU Clermont-Ferrand

CHU Bordeaux

Montpellier (CHU et Clinique Millénaire)

Toulouse (CHU, clinique Pasteur)

Lille (CHU, Hôpital privé le Bois)

Bichat, Massy, CCML, CERIC, Créteil, La Pitié Salpêtrière, Parly 2, HEGP, IMM, Saint-Denis

CHU Strasbourg

CHU Nancy

CHU Besançon

Lyon (HLP, clinique du Tonkin)

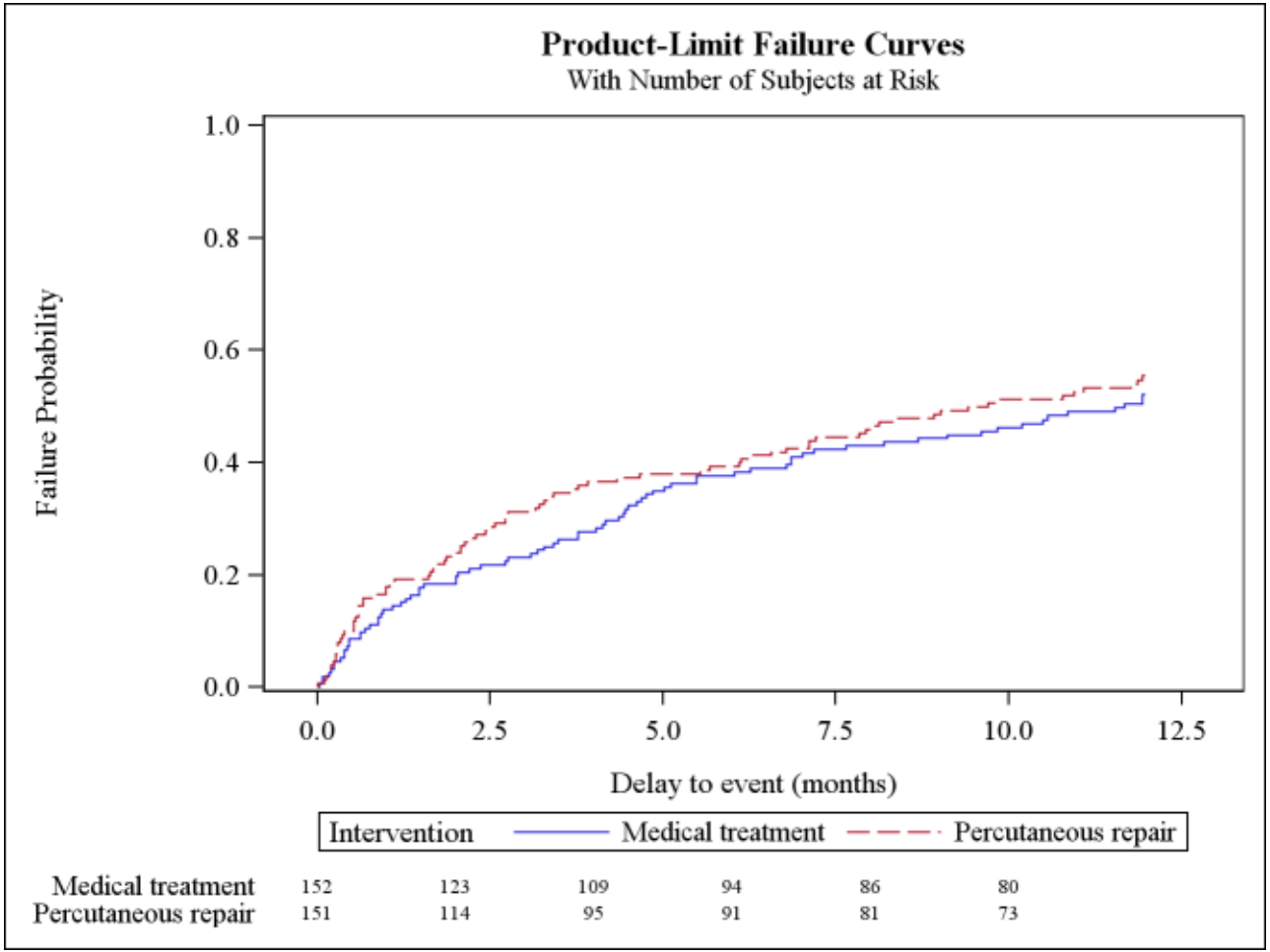
CHU St Etienne

CHU Grenoble

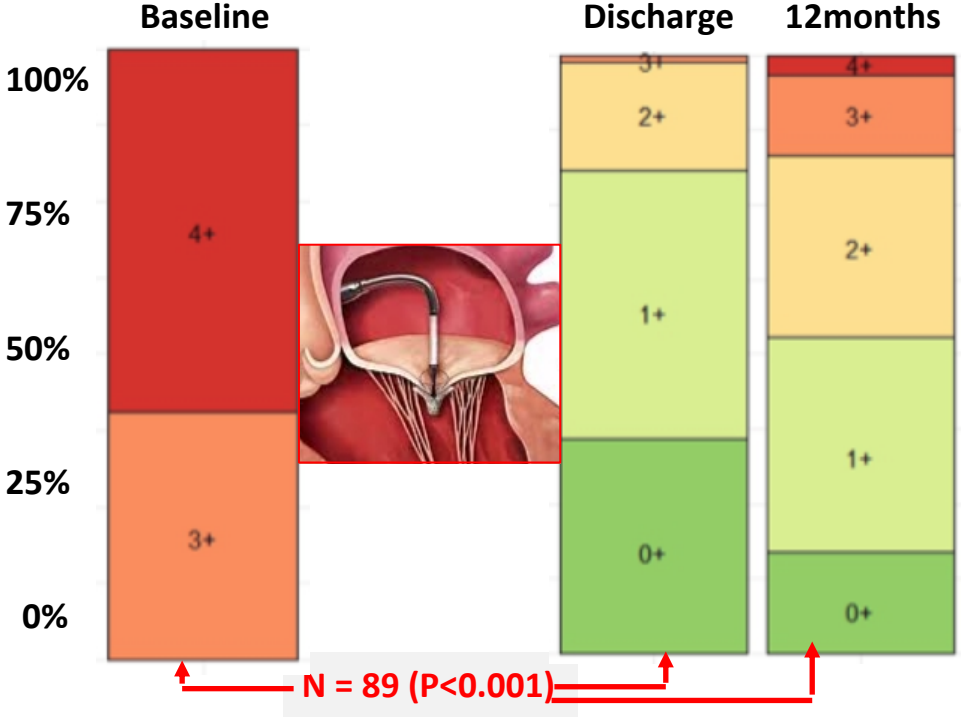
Institut A. Tzanck

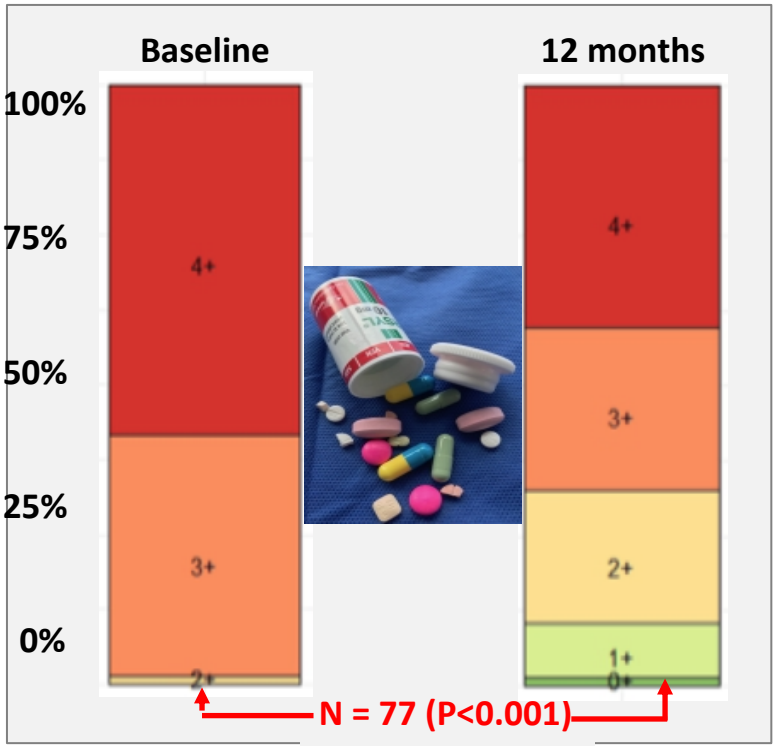
Marseille (La Timone, Saint Joseph, Clairval)

Mitra.fr


Product-Limit Failure Curves
With Number of Subjects at Risk
Failure Probability
1.0
0.8
0.6
0.4
0.2
0.0
0.0
2.5
5.0
7.5
10.0
12.5
Delay to event (months)
Intervention
Medical treatment
Percutaneous repair
Medical treatment 152 123 109 94 86 80
Percutaneous repair 151 114 95 91 81 73

MR grade evolution in both groups (*paired data)*

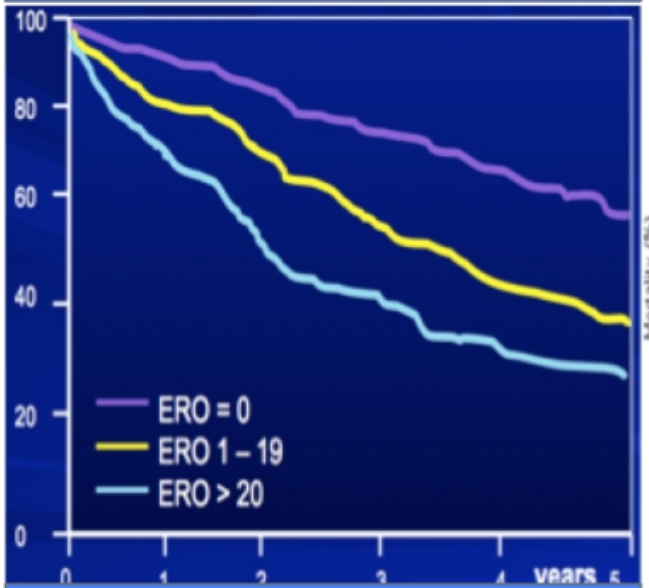




P< 0.001

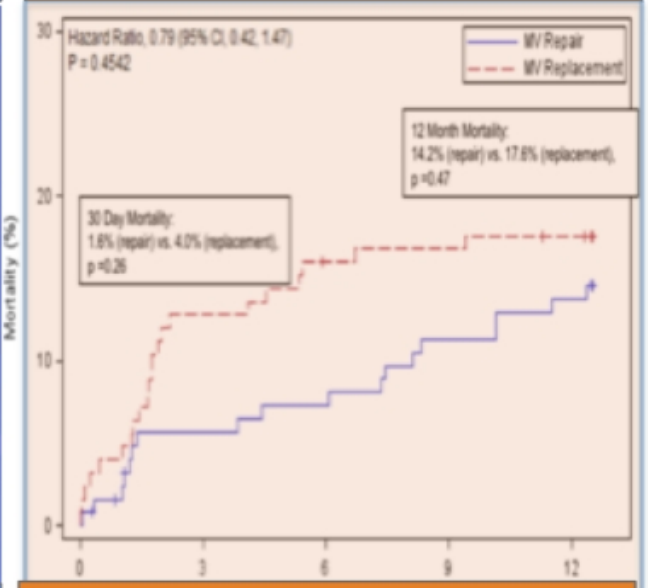
Background

Poor prognosis of 2ary MR



Grigioni et al. Circulation 2001

Repair versus Replacement



Acker et al. NEJM 2014

More than 1000 total publications on MitraClip therapy

Feldman et al. NEJM 2007