

RESHAPE-HF2 Trial

Randomized Investigation of the MitraClip Device in Heart Failure: 2nd Trial in Patients with Clinically Significant Functional Mitral Regurgitation

Stefan D. Anker, MD PhD on behalf of the RESHAPE-HF2 Steering Committee, Trial Committees, Investigators & Coordinators

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Research Contracts:

- Abbott Laboratories, CSL/Vifor

Consulting/Royalties/Owner/Stockholder of healthcare company:

- Personal fees from Actimed, Astra Zeneca, Bayer, Boehringer Ingelheim, Brahms, Cardiac Dimensions, Cardior, Cordio, CSL/Vifor, CVRx, Cytokinetics, Edwards, Farraday Pharmaceuticals, GSK, Impulse Dynamics, Medtronic, Novartis, Novo Nordisk, Occlutech, Pfizer, Regeneron, Relaxera, Repairon, Scirent, Sensible Medical, Vectorious, and V-Wave, all outside of the work presented here.

- Named co-inventor of two patent applications regarding MR-proANP (DE 102007010834 & DE 102007022367), but he does not benefit personally from the related issued patents.

RESHAPE-HF2 (IIT structure)

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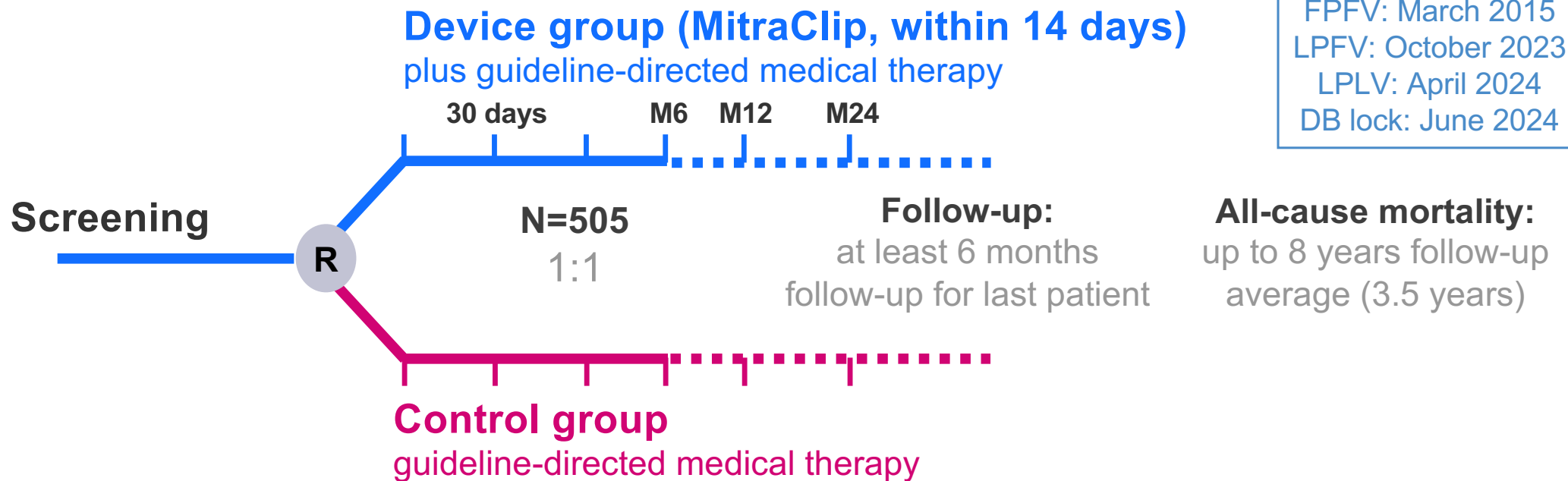
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Legal Sponsor: University Medical Center, Göttingen (UMG) Germany
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CROs: Study Center, UMG Göttingen – MTA Swiss
Statistical Support: Dept of Biostatistics (Lead: Prof. Tim Friede)
Sites: 30 sites in 9 countries

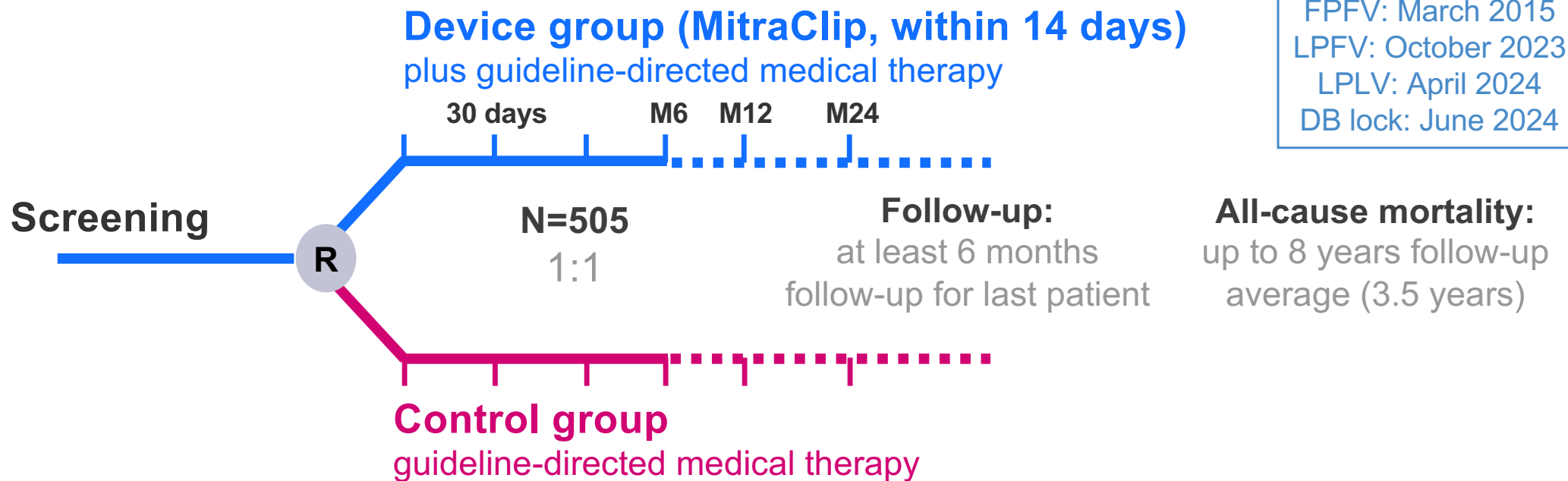


RESHAPE-HF2 – testing MitraClip in the 3rd population



- Symptomatic CHF in NYHA functional class II–IV with LVEF 20–50% [if NYHA II, with NYHA III/IV in last 6mo]
- Clinically significant functional mitral regurgitation (FMR 3+ / 4+ according to European Association of Echocardiography) within 90d prior to randomization & confirmed by the Echo Core-Lab (within 48hrs)
- Hospitalization for HF within 12mo OR BNP ≥ 300 pg/mL or NT-proBNP ≥ 1000 pg/mL within 90d
- Ambulatory and suitable for MC procedure and able to complete a 6-min-WT

RESHAPE-HF2 – testing MitraClip in the 3rd population



FPFV: March 2015
LPFV: October 2023
LPLV: April 2024
DB lock: June 2024

Statistics:

- Primary EPs:
 - (i) Recurrent events of CV death & HHF
 - (ii) Recurrent events of HHF
 - (iii) KCCQ (change BL to 12mo)
 - Secondary EPs: - 6MWT-distance (change BL–12mo)
(Hochberg) - ACM (all available FU) - Recurrent hospitalization (any)
- NYHA class I/II (24mo) - Grade 2+ or less MR (12mo)
- Alpha = 0.05
Significance level controlled
using Hochberg procedure

Anker SD et al.
Reshape-HF2 Design.
EJHF 2024

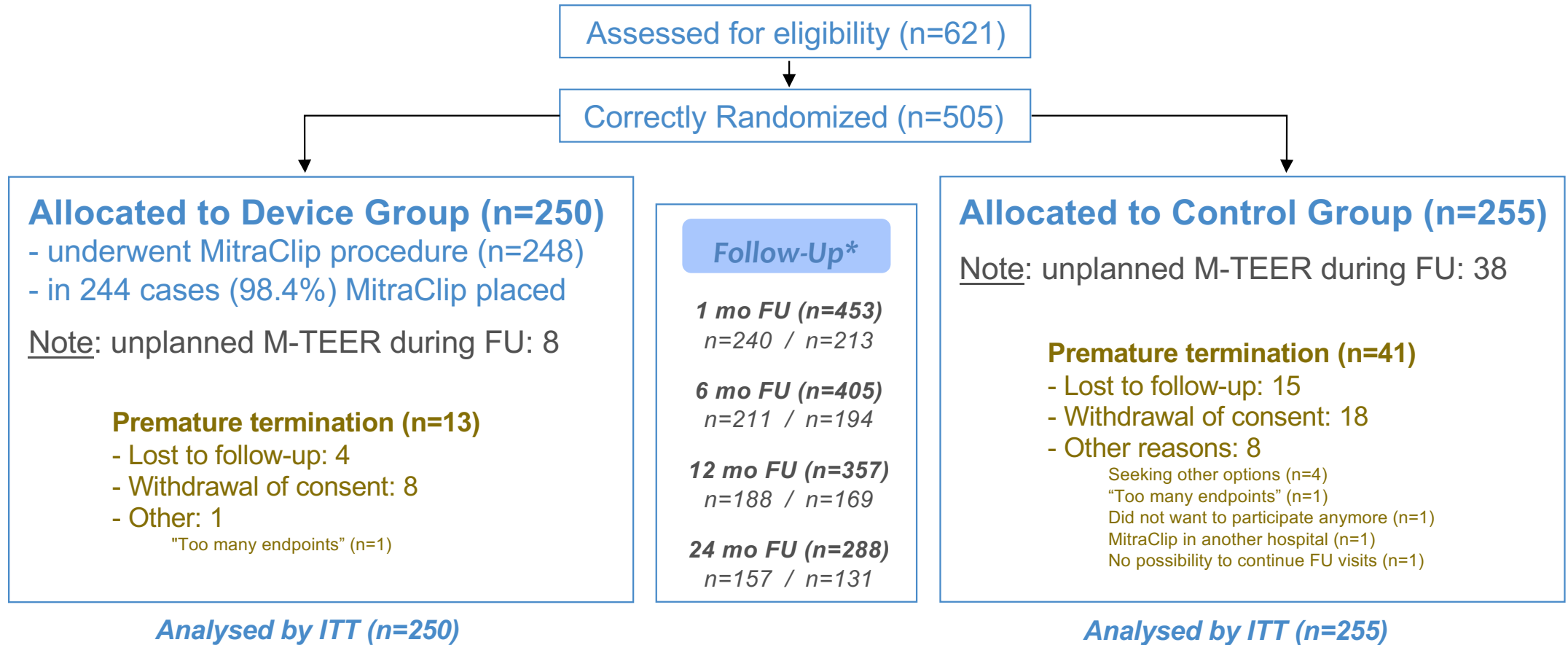
Demographics and Baseline Characteristics

	Device Group (n=250)	Control Group (n=255)
Age (yr)	70.0 ± 10.4	69.4 ± 10.7
Women (%)	55 (22)	44 (17)
Diabetes mellitus (%)	91 (36)	85 (33)
Non-ischaemic HF (%)	88 (35)	88 (35)
NYHA functional class II / III / IV (%)	24 / 60 / 16	26 / 60 / 14
Systolic blood pressure (mm Hg)	112 ± 16	113 ± 16
Atrial fibrillation	118 (47)	125 (49)
Glomerular filtration rate (mL/min/1.73 m ²)	54.9 ± 19.0	56.7 ± 23.3
Therapies of interest at baseline		
RAASi ± ARNI (%)	210 (84)	204 (80)
MRA (%)	200 (80)	215 (84)
Beta blocker (%)	238 (95)	246 (96)
SGLT2-inhibitor (%)	24 (10)	22 (9)
Diuretics (%)	239 (96)	243 (95)
Previous CRT therapy (%)	77 (31)	68 (27)

Demographics and Baseline Characteristics (2)

	Device Group (n=250)	Control Group (n=255)
Hospitalization for HF in previous year (%)	165 (66)	168 (66)
6-min walk distance, median & IQR (m)	300 (220–382)	310 (200–378)
KCCQ-OS score, median & IQR (points)	42.2 (28.3–62.0)	44.3 (25.8–64.2)
NT-proBNP level, median & IQR (pg/mL)	2651 (1630–4918)	2816 (1306–5496)
BNP level, median & IQR (pg/mL)	556 (312–1018)	406 (231–874)
Echocardiography results		
LVEF, median & IQR (%)	32 (26–37)	31 (25–37)
LVEDV, median & IQR (mL)	200 (153–249)	206 (158–250)
LVEDD, median & IQR (cm)	6.9 (6.3–7.6)	6.8 (6.4–7.5)
Effective regurgitant orifice area (EORA), median & IQR (cm ²)	0.23 (0.20–0.30)	0.23 (0.19–0.29)
Regurgitant volume, median & IQR (mL)	35.4 (28.9–43.9)	35.6 (28.2–42.5)
Severity of mitral regurgitation — no. (%)		
Grade 3+	141 (56)	141 (55)
Grade 4+	109 (44)	114 (45)

Patient Disposition & Follow-up



*Follow-up times for 24 months assessments:

- Overall: median 24.0 months (IQR 12.0–25.0); Device group: 24.2 (IQR 15.7–25.0); Control group: 23.6 (IQR 10.4–24.9).

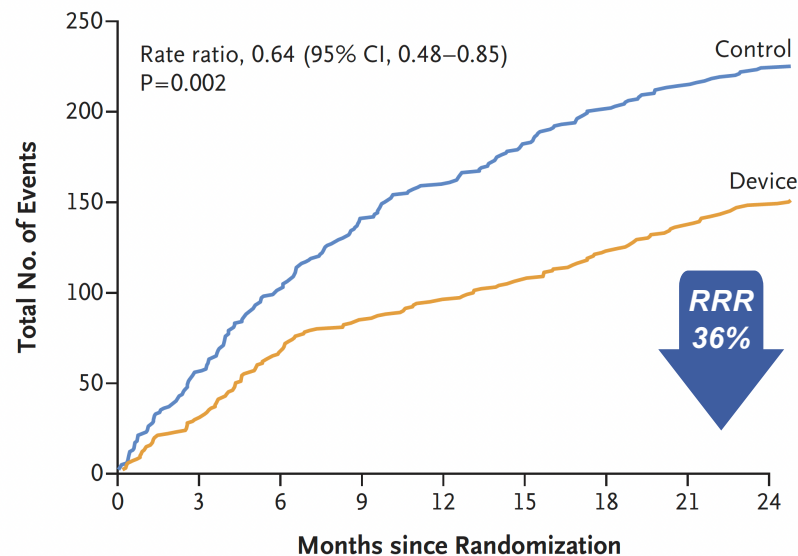
Follow-up times for all-cause mortality assessment:

- Overall: median 29.4 months (IQR 14.0–61.1); Device group: 34.3 (IQR 16.0–63.1); Control group: 27.0 (IQR 11.6–58.0)

Primary Endpoint 1: Recurrent HHF or CV death within 24 months

Primary Endpoint 2: Recurrent HHF within 24 months

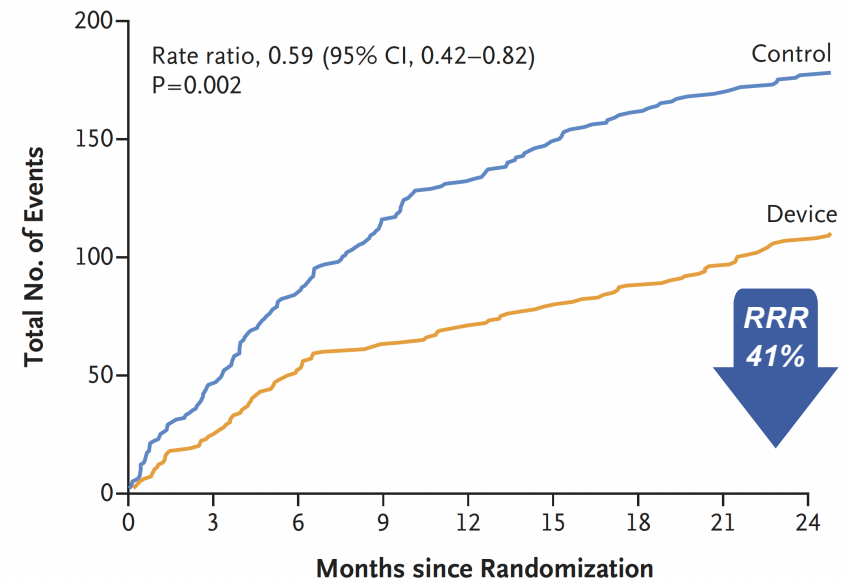
Composite of Hospitalization for Heart Failure or Death from Cardiovascular Causes



No. at Risk

Control	255	240	223	204	189	179	165	155	146
Device	250	241	222	207	197	191	179	170	163

Hospitalization for Heart Failure

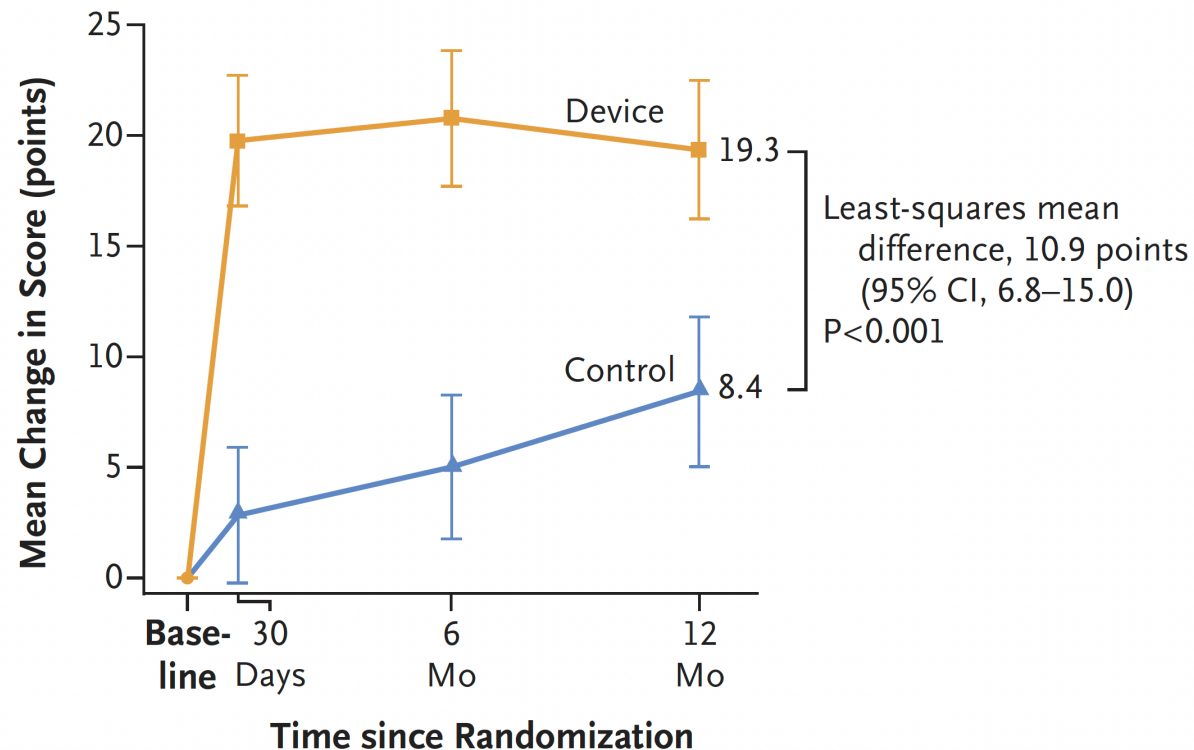


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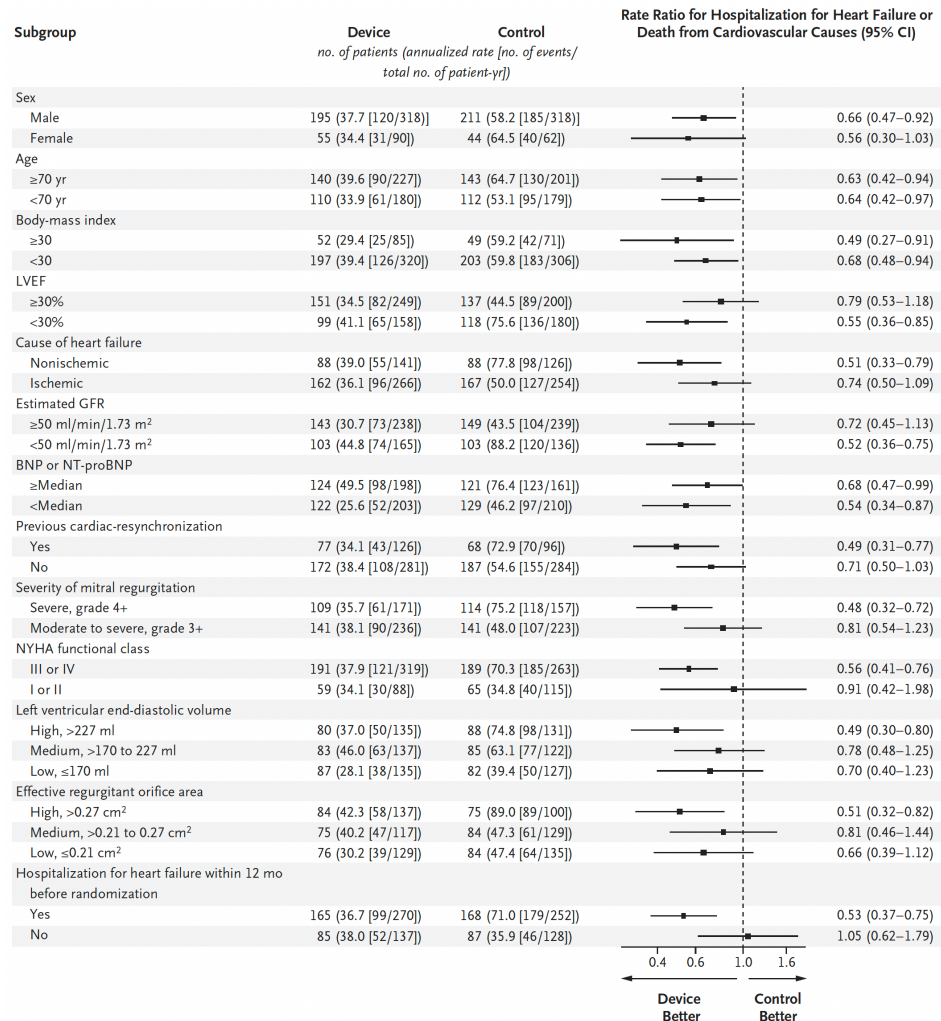
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Primary Endpoint 3 – Change from baseline over a period of 12 months in the KCCQ–Overall Summary score for QoL

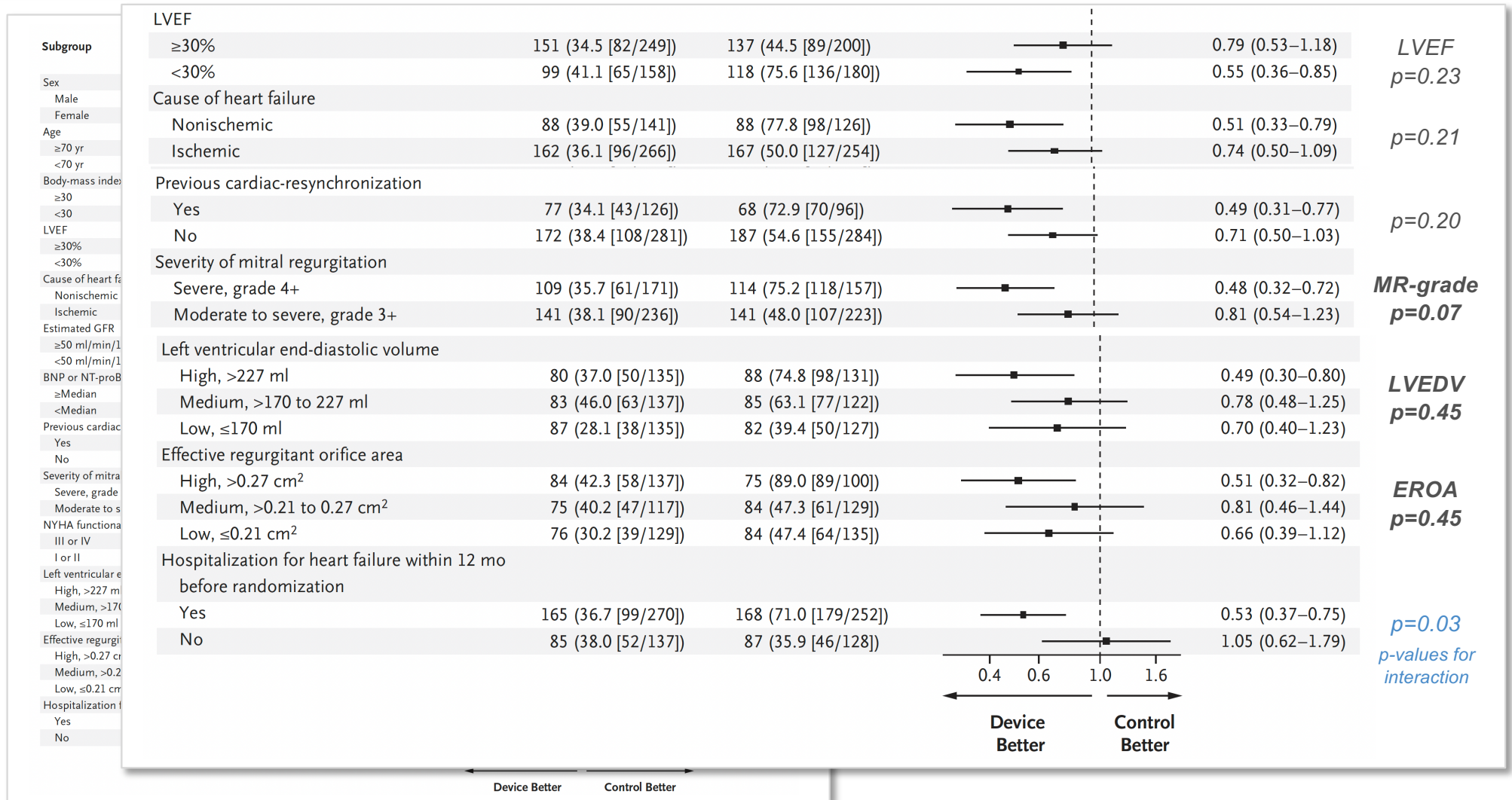
KCCQ-OS Score



Subgroup results for Primary Endpoint 1 (HHF & CVD)



Subgroup results for Primary Endpoint 1 (HHF & CVD)



Secondary Endpoints

Secondary end points				
Mitral regurgitation grade $\leq 2+$ at 12 mo — no./total no. (%)	132/146 (90.4)	43/119 (36.1)**	21.3 (10.7–45.8) ^{††}	<0.001 [¶]
Mean change in 6-min walk distance from baseline to 12 mo — m	34.0 $\pm$ 105.9	5.1 $\pm$ 97.6	20.5 (0.3–40.7)	0.05 ^{‡‡}
Rate of death from any cause during the complete* follow-up per 100 patient-yr (no. of events/total no. of patient-yr)	17.0 (142/836.7)	18.6 (142/765.2)	0.90 (0.71–1.13)	0.37
Rate of recurrent hospitalization for any cause during 24 mo per 100 patient-yr (no. of events/total no. of patient-yr)	48.7 (199/408.6)	61.0 (233/381.9)	0.82 (0.63–1.07)	0.15
NYHA functional class I or II heart failure at 12 mo — no./total no. (%) ^{§§}	140/188 (74.5)	96/164 (58.5)	2.35 (1.48–3.77) ^{††}	<0.001 [¶]

***Follow-up times for 24 months assessments:**

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Adverse events during 24 months follow-up

Event	Device Group (N = 250)	Control Group (N = 255)	Hazard or Rate Ratio (95% CI) [†]	P Value
<i>no. of patients with event (estimate of event rate)</i>				
Death from any cause [‡]	51 (22.3)	67 (29.6)	0.73 (0.51–1.05)	0.09
Death from cardiovascular causes§	41 (17.8)	47 (20.4)	0.84 (0.55–1.28)	0.43
Death from noncardiovascular causes§	10 (4.5)	20 (9.3)	0.46 (0.22–0.99)	0.04
Unplanned MitraClip implantation¶	8 (2.0)	25 (6.5)	0.32 (0.14–0.70)	0.004
All unplanned transcatheter mitral-valve repair¶	8 (2.0)	38 (10.0)**	0.21 (0.10–0.44)	<0.001
Mitral-valve surgery ^{††}	1 (0.004)	2 (0.008)	0.51 (0.05–5.58)	0.57
PCI§	6 (0.026)	8 (0.034)	0.74 (0.26–2.12)	0.57
CABG	0	0	—	—
Stroke§	5 (0.022)	2 (0.008)	2.5 (0.48–12.9)	0.25
Myocardial infarction¶	3 (0.007)	3 (0.008)	1.02 (0.14–7.52)	0.99
LVAD implantation ^{†††}	1 (0.008)	2 (0.02)	0.5 (0.05–5.49)	0.56
Heart transplantation	1	0	—	—
Implantation of ICD or CRT-D§	7 (1.8)	7 (1.7)	0.96 (0.35–2.66)	0.93

Success on all 3 primary endpoints & more

Primary Endpoints



Rate of heart failure hospitalizations or CV death (at 24 months)

36% ↓ in risk
P = 0.002



Rate of recurrent heart failure hospitalizations (at 24 months)

41% ↓ in risk
P = 0.002



KCCQ overall summary score (at 12 months)

11 point ↑ in QoL
P < 0.0001

Secondary Endpoints



NYHA class I/II (at 12 months)

2.35 more likely
P < 0.0001



6min-walking test distance (at 12 months)

20.5 m ↑ performance
P = 0.046

Limitations

Although randomization was performed in a blinded manner, the participants, investigators, and echocardiographers were not unaware of subsequent treatments. This situation could have created bias, especially for quality-of-life assessments recorded by patients.

Some patients who had been assigned to receive medical therapy alone underwent transcatheter mitral-valve repair, which could have affected the observed treatment effect.

Finally, the trial was not designed to show differences in mortality.

Conclusions

Among patients with heart failure with moderate to severe functional mitral regurgitation who received medical therapy, the addition of transcatheter mitral-valve repair led to a lower rate of all hospitalization for heart failure (first & recurrent) or cardiovascular death and to a lower rate of all hospitalization for heart failure alone at 24 months and to a better quality of life at 12 months compared to medical therapy alone.

A broader application of M-TEER for heart failure with functional mitral regurgitation of less than severe disease grade may be appropriate and deserves further study.



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ORIGINAL ARTICLE

Transcatheter Valve Repair in Heart Failure with Moderate to Severe Mitral Regurgitation

S.D. Anker, T. Friede, R.S. von Bardeleben, J. Butler, M.S. Khan, M. Diek, J. Heinrich, M. Geyer, M. Placzek, R. Ferrari, W.T. Abraham, O. Alfieri, A. Auricchio, A. Bayes-Genis, J.G.F. Cleland, G. Filippatos, F. Gustafsson, W. Haverkamp, M. Kelm, K.-H. Kuck, U. Landmesser, A.P. Maggioni, M. Metra, V. Ninios, M.C. Petrie, T. Rassaf, F. Ruschitzka, U. Schäfer, P.C. Schulze, K. Spargias, A. Vahanian, J.L. Zamorano, A. Zeiher, M. Karakas, F. Koehler, M. Lainscak, A. Öner, N. Mezilis, E.K. Theofilogiannakos, I. Ninios, M. Chrissoheris, P. Kourkouveli, K. Papadopoulos, G. Smolka, W. Wojakowski, K. Reczuch, F.J. Pinto, Ł. Wiewiórka, Z. Kalarus, M. Adamo, E. Santiago-Vacas, T.F. Ruf, M. Gross, J. Tongers, G. Hasenfuss, W. Schillinger, and P. Ponikowski, for the RESHAPE-HF2 Investigators*

Additional information with a focus on hospitalization events

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Hospitalization of Symptomatic Patients With Heart Failure and Moderate-to- Severe Functional Mitral Regurgitation Treated With MitraClip

Insights From RESHAPE-HF2

Ponikowski P, Friede T, von Bardeleben RS et al.