ESC European Society of Cardiology

European Heart Journal (2019) **40**, 2189–2193
doi:10.1093/eurheartj/ehz222

VIEWPOINT
Valvular heart disease

Mitral regurgitation in heart failure: time for a rethink

Fabien Praz[1], Carmelo Grasso[2], Maurizio Taramasso[3], Andreas Baumbach[4,5], Nicolo Piazza[6], Corrado Tamburino[2], Stephan Windecker[1], Francesco Maisano[3], and Bernard Prendergast[7]*

[1]Department of Cardiology, Bern University Hospital, University of Bern, Freiburgstrasse, 3011 Bern, Switzerland; [2]Thoracic-Vascular Department, Azienda Ospedaliero-Universitaria "Policlinico-Vittorio Emanuele", Via S. Sofia, 78, 95123 Catania, Italy; [3]University Hospital of Zurich, Department of Cardiac Surgery, University of Zurich, Rämistrasse 100, 8006 Zurich, Switzerland; [4]Barts Heart Centre, Barts Health NHS, W Smithfield, London EC1A 7BE, UK; [5]Queen Mary University London, Mile End Rd, Bethnal Green, London E1 4NS, UK; [6]Division of Cardiology, Department of Medicine, McGill University Health Centre, 1001 Decarie Blvd, Montreal (Qc) H4A 3J1, Canada; and [7]Department of Cardiology, St. Thomas' Hospital, Westminster Bridge Rd, Lambeth, London SE1 7EH, UK

Received 29 October 2018; revised 27 December 2018; editorial decision 27 March 2019; accepted 28 March 2019; online publish-ahead-of-print 21 April 2019

Secondary (or functional) mitral regurgitation (MR) frequently accompanies heart failure syndromes and is associated with poor prognosis.[1] Initial surgical approaches[2] failed to impact on outcome in contrast with optimized medical therapy, cardiac resynchronization therapy (CRT), long-term ventricular assist devices, and cardiac transplantation. Valve surgery remains challenging in this setting, with inferior outcomes than in primary (or degenerative) MR, and the indications and choice of technique are not supported by robust evidence.[3] Transcatheter treatment of primary and secondary MR has emerged as an alternative using a variety of approaches. Of these, the most widely adopted has been edge-to-edge repair using the MitraClip device (Abbott Vascular). However, despite application in >70 000 patients since 2003 and favourable evidence compared with surgery in patients with mainly primary MR (73%),[4] there have been no published randomized studies focusing on subjects with secondary MR. Until now.

The MITRA-FR trial

In this French study, presented and simultaneously published in late August 2018,[5] 307 patients with systolic heart failure (ejection fraction 15–40%) and severe functional MR [effective regurgitant orifice area (EROA) >20 mm^2 or regurgitant volume >30 mL/beat] were randomly assigned to edge-to-edge MitraClip repair plus optimal medical treatment or optimal medical treatment alone. Heart failure was of ischaemic origin in 59% and CRT used in 27%. Baseline medical treatment was similar in both groups although changes in medication were not monitored during follow-up.

Edge-to-edge repair achieved reduction of MR to Grade 2+ or less according to ESC/EACTS guidelines[3] in 92% of patients at the time of hospital discharge but had no impact on the primary outcome of all-cause mortality or heart failure re-hospitalization at 1-year follow-up [54.6 vs. 51.3%, odds ratio (OR) 1.16; 95% condolence interval (CI) 0.73–1.84; $P = 0.53$]. Rates of all-cause mortality [24.3% vs. 22.4%, hazard ratio (HR) 1.11; 95% CI 0.69–1.77] and heart failure re-hospitalization (48.7% vs. 47.4%, HR 1.13; 95% CI 0.81–1.56) were also similar. Estimates of secondary outcomes were imprecise owing to incomplete follow-up data (including echocardiographic findings, functional status, biomarker, and quality of life outcomes).

The COAPT trial

This US trial, presented and simultaneously published only 4 weeks later,[6] randomly assigned 614 patients with symptomatic systolic heart failure (left ventricular ejection fraction 20–50%) and moderate-to-severe or severe functional MR [semi-quantitative Grade 3+ or 4+ according to integrative assessment as defined by the American Society of Echocardiography[7]] to edge-to-edge MitraClip repair plus optimal medical treatment or optimal medical treatment alone. Eligibility was confirmed by an echocardiographic core laboratory and a central committee supervised the implementation of maximal medical treatment (including CRT if appropriate). Heart failure was of ischaemic origin in 61% and CRT used in 36%.

Edge-to-edge repair (mean 1.7 ± 0.7 clips) was successful in 98% of patients, with reduction in peri-procedural MR to ≤ Grade 2+ according to AHA/ACC Guidelines[8] in 95% that was maintained in survivors at 2-year follow-up. Importantly, the procedure was safe with freedom from device-related complications in 97% at 1 year (exceeding the pre-specified performance goal of 88%). MitraClip implantation was associated with substantial reduction in the primary endpoint [hospitalization for heart failure 35.8% vs. 67.9% per patient-year: HR 0.53, 95% CI 0.40–0.70; $P < 0.001$; number needed to treat (NNT) 3.1, 95% CI 1.9–7.9] and every 1 of 10 pre-specified,

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

* Corresponding author. Tel: 020 7188 1047, Email: bernard.prendergast@gstt.nhs.uk

Table 1 Key differences between the COAPT and MITRA-FR trials

		MITRA-FR	COAPT
	Primary endpoint	All-cause death and hospitalization for CHF at 1 year	All hospitalizations for CHF within 2 years (including recurrent events)
Key exclusion criteria	Heart failure severity	NYHA class <II	NYHA class <II ACC/AHA Stage D heart failure
	Left ventricular dimensions	No exclusion criteria	LVESD >70 mm
	Coronary artery disease	CABG or PCI performed within 1 month	Untreated coronary artery disease requiring revascularization
	Right ventricle	No exclusion criteria	Right-sided congestive heart failure with moderate or severe right ventricular dysfunction
	Pulmonary disease	No exclusion criteria	COPD with home oxygen therapy or chronic oral steroid use Estimated or measured PAP >70 mmHg
Principal baseline characteristics	Number of patients screened	452	1576
	Number of patients enrolled (ITT)	304	614
	Mean age (years)	70 ± 10	72 ± 12
	Mean LVEF (%)	33 ± 7	31 ± 10
	MR severity (EROA, cm^2)	0.31 ± 0.10	0.41 ± 0.15
	Mean indexed LVEDV (mL/m^2)	135 ± 35	101 ± 34
Safety and efficacy endpoints in the intervention arm	Complications[a] (%)	14.6	8.5
	No implant (%)	9	5
	Implantation of multiple clips (%)	54	62
	Post-procedural MR grade ≤2+ (%)[b]	92	95
	MR grade ≤2+ at 1 year (%)[b]	83	95
	Hospitalization for CHF at 1 year (%)	49	38
	30-Day mortality (%)	3.3	2.3
	1-Year mortality (%)	24	19

[a]MITRA-FR definition of pre-specified serious adverse events: device implant failure, transfusion or vascular complication requiring surgery, ASD, cardiogenic shock, cardiac embolism/stroke, tamponade, and urgent cardiac surgery.
[b]According to ESC/EACTS guidelines[3] in MITRA-FR and AHA/ACC Guidelines[8] in COAPT.
ACC, American College of Cardiology; AHA, American Heart Association; BNP, brain natriuretic peptide; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; EROA, effective regurgitant orifice area; ITT, intention to treat; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAP, pulmonary artery pressure.

statistically powered secondary endpoints [including 2-year all-cause mortality (29.1% vs. 46.1%: HR 0.62, 95% CI 0.46–0.82; $P < 0.001$; NNT 5.9, 95% CI 3.9–11.7) and the composite of death and heart failure re-hospitalization (45.7% vs. 67.9%: HR 0.57, 95% CI 0.45–0.71; $P < 0.001$; NNT 4.5, 95% CI 3.3–7.2)].

Differences between the trials

Key differences in trial design, clinical characteristics, and procedural outcomes may explain the radically different outcomes of these superficially similar studies (*Table 1*, *Figure 1*).

- Varying definitions of MR adopted by the European[3] (MITRA-FR, EROA >20 mm2, or regurgitant volume >30 mL/beat) and US[8] (COAPT Grade 3+ to 4+) guidelines.
- Inclusion of patients with greater left ventricular dilatation in MITRA-FR—those with an end-systolic dimension >70 mm or in Stage D heart failure were excluded from COAPT.
- Inclusion in COAPT required persistent symptoms despite a prolonged run in period on maximal guideline-directed medical treatment. In contrast, intensification of medical treatment was allowed before randomization in MITRA-FR (consistent with 'real-world' practice) although subsequent changes in medication were not monitored during follow-up.
- More frequent peri-procedural complications and inferior durability of the immediate result in MITRA-FR, possibly partially related to less frequent use of multiple clips.
- Lack of power and missing functional and echocardiographic follow-up data in MITRA-FR may have masked secondary endpoint differences.
- Mortality reduction only emerged in the second year after MitraClip edge-to-edge repair in COAPT—this observation may have been shrouded in MITRA-FR owing to shorter follow-up and lack of statistical power.

Take-home messages

COAPT is the first study to demonstrate that transcatheter mitral valve repair can significantly improve survival of selected patients with systolic heart failure and secondary MR who have exhausted

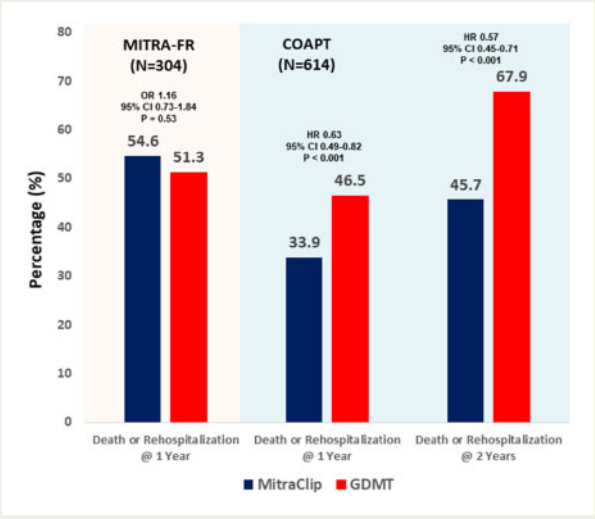

Figure 1 Comparison of MITRA-FR and COAPT trial outcomes. CI, confidence interval; GDMT, guideline-directed medical therapy; HR, hazard ratio; OR, odds ratio.

Table 2 Comparison of relative risk reduction and number needed to treat to prevent one death among the principal heart failure treatment options

Treatment modality	Relative risk reduction for all-cause mortality (%)	NNT for all-cause mortality
ACE inhibitor or ARB[11]	17	22 over 42 months
Beta blocker[11]	34	28 over 12 months
Aldosterone antagonist[11]	30	9 over 24 months
CRT[11]	36	12 over 24 months
Sacubitril/valsartan[12]	16	36 over 27 months
MitraClip[6] (COAPT population)	37	6 over 24 months

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; ICD, implantable cardiac defibrillator; NNT, number needed to treat.

medical treatment options. The study also confirms that these patients have a terrible prognosis despite guideline-directed maximal medical treatment: two-thirds of the control group were admitted with heart failure and nearly 50% had died within 2 years. Severe MR should no longer be regarded as an innocent bystander of underlying ventricular disease but as an important contributor to deleterious outcomes. Given that surgery has limited benefits in this setting[9] and is associated with high peri-operative risk,[10] transcatheter mitral valve repair represents a valuable treatment option for selected patients who remain symptomatic despite optimal medical treatment (*Table 2*).[11,12]

The combined results of both studies provide valuable guidance regarding patient selection. MITRA-FR demonstrates that those with extreme left ventricular dilatation and less severe secondary MR (EROA <30 mm^2) are unlikely to benefit from transcatheter mitral valve repair. This is consistent with an exploratory *post hoc* subgroup analysis of COAPT demonstrating that patients with EROA ≤30 mm^2 and left ventricular end-diastolic volume >96 mL/m^2 (10.2% of the COAPT study population) demonstrate no change in all-cause mortality or heart failure re-hospitalization 1 year after MitraClip implantation (unpublished data presented at TCT 2018). Conversely, the overall outcomes of COAPT demonstrate that those with moderate left ventricular dilatation and more severe MR associated with persistent symptoms despite optimal medical treatment should be offered transcatheter mitral valve repair to improve symptoms and prognosis.

The observation that EROA depends directly on left ventricular dilatation (LVEDV) and function[13] has generated the concept of 'proportionate' and 'disproportionate' MR[14] which may reconcile both studies. Patients with 'disproportionate' MR are those with an EROA greater than expected based on left ventricular parameters and may be more likely to benefit from percutaneous mitral valve repair. Whilst the COAPT trial mainly included such patients, further investigations are needed to define the most appropriate diagnostic tools and thresholds to differentiate these clinical phenotypes.

Careful echocardiographic screening of heart failure populations before and after the instigation of optimal medical treatment will therefore be essential to identify suitable candidates and determine the appropriate timing of transcatheter intervention. Whilst the results of MITRA-FR indicate that patients with very advanced left ventricular dilatation do not respond to edge-to-edge MitraClip repair, the findings of COAPT demonstrate that earlier treatment is beneficial in those with moderate left ventricular dilatation and more severe MR. Further studies are required to determine whether patients with marked left ventricular dilatation *and* severe MR might benefit from edge-to-edge repair, since this group was under-represented in MITRA-FR and excluded from COAPT.

Clinical and regulatory consequences in Europe and the USA

A notable feature of COAPT was the rigorous patient selection process based on randomization after a prolonged run in period on maximally tolerated guideline-directed medical therapy, followed by continued monitoring of medication throughout the trial, thereby mitigating the potential bias of medical therapy in either arm. Translation of the impressive outcomes to everyday clinical practice will require that patients with secondary MR are on optimal medical treatment prior to consideration of edge-to-edge repair, as already recommended in the ESC/EACTS guidelines.[8] In turn, this reinforces the role of the Heart Team (particularly heart failure specialists) in the management of patients with secondary MR.

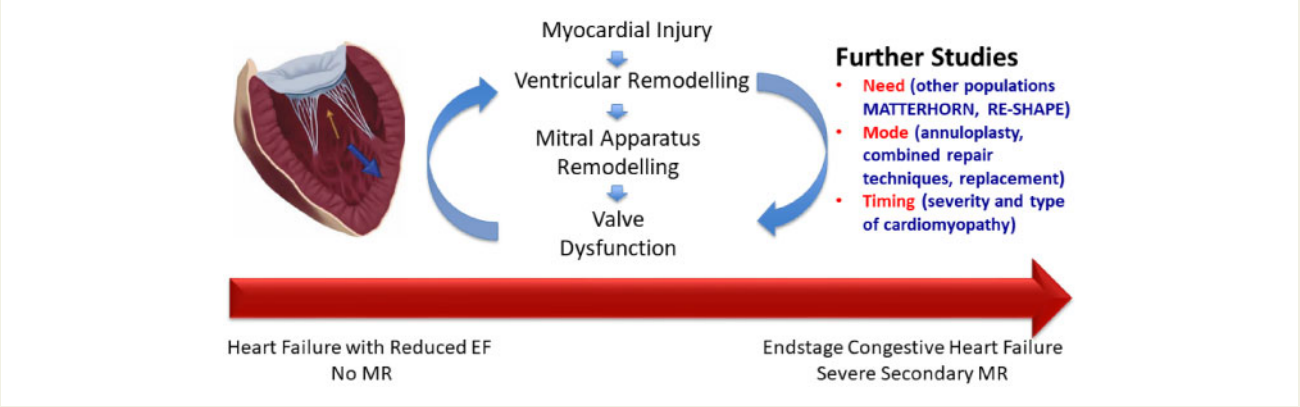

Figure 2 Unanswered questions in secondary mitral regurgitation: the need, mode, and timing of intervention. EF, ejection fraction; MR, mitral regurgitation.

The MitraClip device received CE mark approval for high-risk patients with primary or secondary MR in 2008 and US FDA approval for high-risk patients with primary MR 5 years later. Approximately 65% of procedures in Europe are currently performed for secondary MR—conversely, 80% in the USA are for primary MR. Whilst the number of patients with secondary MR is large (~2.4 million in the USA alone), the proportion eligible for MitraClip according to COAPT criteria may be limited given the high proportion of patients who were ineligible for the study and resulting slow recruitment. Careful adherence to the inclusion and exclusion criteria of MITRA-FR and COAPT will be required to avoid chaotic expansion of transcatheter mitral valve repair and an excess of expensive futile procedures. Lack of reimbursement strategies and appropriate care pathways may be further important obstacles to market penetration.

Unanswered questions and ongoing trials—implications for future study design

Detailed secondary endpoint analysis, longer-term follow-up of the randomized cohorts and pooled analysis of individual patient level data will help to refine patient selection and determine the optimal timing of intervention before the onset of severe left ventricular dilatation (*Figure* 2). The ongoing European RESHAPE-HF-2 study will provide important complementary information by enrolling patients with different left ventricular ejection fraction thresholds according to symptomatic status [New York Heart Association (NYHA) Class II: 15–35%; NYHA Class III/IV: 15–45%] and excluding those who have a walking distance greater than 475 m or are unable to perform a 6-min walk test. Meanwhile, the MATTERHORN trial is comparing the merits of transcatheter edge-to-edge repair with surgery in patients at high surgical risk with a left ventricular ejection fraction ≥20%. The suggestion that future clinical trials in secondary MR may require a MitraClip control arm will have significant impact on the progress and development of transcatheter mitral valves, annuloplasty devices and other edge-to-edge systems.[15]

Future research will also be required to investigate the durability of edge-to-edge repair, compare new clip designs (and other transcatheter techniques) with new medical therapies, and evaluate algorithms for patient selection and post-procedural care incorporating advanced imaging techniques and novel serum biomarkers.

Improved collaboration between the specialities of interventional cardiology, imaging, and heart failure: educational and strategic goals

The landmark COAPT results demonstrate the important synergy of medical and device therapy and suggest that best outcomes are achieved by integration of both approaches, while MITRA-FR provides key information concerning the appropriate time window for intervention. Close two-way collaboration between interventional cardiology and heart failure communities is the only way to guarantee that this is achieved and constructive education programmes are fundamentally important at this juncture. Dedicated training for interventional cardiologists engaged in mitral intervention and sufficient case volume to avoid adverse events during the learning curve will be essential. Clinicians and imaging specialists should place greater emphasis on the assessment of secondary MR in heart failure patients and consider early referral of those with continued symptoms despite maximal tolerated guideline-directed medical treatment for specialist assessment with a view to edge-to-edge repair. Furthermore, alternative means of transcatheter repair or replacement are needed for patients who are anatomically unsuitable for MitraClip placement (ideally within the remit of future studies). Conversely, the current trend to restrict transcatheter mitral repair techniques to end stage heart failure patients with severe left ventricular dilatation and lesser degrees of MR needs to be curtailed. Earlier treatment of severe secondary MR is key to improve survival and reduce cumulative heart failure episodes that are associated with recurrent (and expensive) hospitalization and dramatic reduction in functional capacity and

quality of life. Finally, the divisions between medical and device therapy in heart failure (and their protagonists) need to be abandoned. A new era of genuine synergistic collaboration between the two disciplines has dawned—with greater awareness of the pathophysiological importance of secondary MR and the interests of patients as its focus.

Conflict of interest: F.P. has received consulting fees from Edwards Lifesciences; C.G. is a proctor physician for Abbott Vascular; M.T. is a consultant for Abbott Vascular and 4 Tech; A.B. has received institutional grant support and has served on the advisory board for Abbott Vascular, MicroPort, Cardinal Health, and Sinomed and has received speaker fees from Keystone Heart and AstraZeneca; N.P. has been a consultant/proctor for HighLife, Medtronic, MicroPort, and Cephea. C.T. has received honoraria/lecture fees from Abbott Vascular and Medtronic. S.W. has received research grants to the institution from Abbott, Amgen, Boston Scientific, Biotronik, and St. Jude Medical. F.M. has served as a consultant for Edwards Lifesciences, Medtronic, St. Jude Medical, Abbott Vascular, and Valtech and has received royalties from Edwards Lifesciences. B.P. has received unrestricted research grants from Edwards Lifesciences and lecture fees from Edwards Lifesciences and Boston Scientific.

References

1. Goliasch G, Bartko PE, Pavo N, Neuhold S, Wurm R, Mascherbauer J, Lang IM, Strunk G, Hulsmann M. Refining the prognostic impact of functional mitral regurgitation in chronic heart failure. *Eur Heart J* 2018;**39**:39–46.
2. Bolling SF, Pagani FD, Deeb GM, Bach DS. Intermediate-term outcome of mitral reconstruction in cardiomyopathy. *J Thorac Cardiovasc Surg* 1998;**115**:381–386; discussion 7–8.
3. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;**38**:2739–2791.
4. Feldman T, Kar S, Elmariah S, Smart SC, Trento A, Siegel RJ, Apruzzese P, Fail P, Rinaldi MJ, Smalling RW, Hermiller JB, Heimansohn D, Gray WA, Grayburn PA, Mack MJ, Lim DS, Ailawadi G, Herrmann HC, Acker MA, Silvestry FE, Foster E, Wang A, Glower DD, Mauri L; EVEREST II Investigators. Randomized comparison of percutaneous repair and surgery for mitral regurgitation: 5-year results of EVEREST II. *J Am Coll Cardiol* 2015;**66**:2844–2854.
5. Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, Lefevre T, Piot C, Rouleau F, Carrie D, Nejjari M, Ohlmann P, Leclercq F, Saint Etienne C, Teiger E, Leroux L, Karam N, Michel N, Gilard M, Donal E, Trochu JN, Cormier B, Armoiry X, Boutitie F, Maucort-Boulch D, Barnel C, Samson G, Guerin P, Vahanian A, Mewton N; MITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med* 2018;**379**:2297–2306.
6. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, Rajagopal V, Sarembock IJ, Brieke A, Marx SO, Cohen DJ, Weissman NJ, Mack MJ; COAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018;**379**:2307–2318.
7. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, Hahn RT, Han Y, Hung J, Lang RM, Little SH, Shah DJ, Shernan S, Thavendiranathan P, Thomas JD, Weissman NJ. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* 2017;**30**:303–371.
8. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin VH, Sundt TM, Thompson A. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017;**70**:252–289.
9. Wu AH, Aaronson KD, Bolling SF, Pagani FD, Welch K, Koelling TM. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. *J Am Coll Cardiol* 2005;**45**:381–387.
10. Andalib A, Chetrit M, Eberg M, Filion KB, Theriault-Lauzier P, Lange R, Buithieu J, Martucci G, Eisenberg M, Bolling SF, Piazza N. A systematic review and meta-analysis of outcomes following mitral valve surgery in patients with significant functional mitral regurgitation and left ventricular dysfunction. *J Heart Valve Dis* 2016;**25**:696–707.
11. Fonarow GC, Yancy CW, Hernandez AF, Peterson ED, Spertus JA, Heidenreich PA. Potential impact of optimal implementation of evidence-based heart failure therapies on mortality. *Am Heart J* 2011;**161**:1024–1030.e3.
12. Prenner SB, Shah SJ, Yancy CW. Role of angiotensin receptor-neprilysin inhibition in heart failure. *Curr Atheroscler Rep* 2016;**18**:48.
13. Grayburn PA, Carabello B, Hung J, Gillam LD, Liang D, Mack MJ, McCarthy PM, Miller DC, Trento A, Siegel RJ. Defining "severe" secondary mitral regurgitation: emphasizing an integrated approach. *J Am Coll Cardiol* 2014;**64**:2792–2801.
14. Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. *JACC Cardiovasc Imaging* 2019;**12**:353–362.
15. Praz F, Spargias K, Chrissoheris M, Bullesfeld L, Nickenig G, Deuschl F, Schueler R, Fam NP, Moss R, Makar M, Boone R, Edwards J, Moschovitis A, Kar S, Webb J, Schafer U, Feldman T, Windecker S. Compassionate use of the PASCAL transcatheter mitral valve repair system for patients with severe mitral regurgitation: a multicentre, prospective, observational, first-in-man study. *Lancet* 2017;**390**:773–780.