

## Cardiovascular Topics

# Is there a role for combination anti-remodelling therapy for heart failure secondary to chronic rheumatic mitral regurgitation?

Ruchika Meel, Ferande Peters, Elena Libhaber, Mohammed R Essop

### Abstract

**Introduction:** The value of combination anti-remodelling therapy for heart failure (HF) secondary to mitral regurgitation (MR) is unknown. We studied the effect of anti-remodelling therapy on clinical and echocardiographic parameters in patients with severe chronic rheumatic mitral regurgitation (CRMR) presenting in HF.

**Methods:** Thirty-one patients (29 females) at Chris Hani Baragwanath Academic Hospital, treated with combination therapy for HF due to CRMR and New York Heart Association functional class II–III symptoms, underwent prospective six-month follow up.

**Results:** Mean age was  $50.7 \pm 8.5$  years. No patients died or were hospitalised for HF during the study period. No worsening of clinical symptoms or functional status, or left and right ventricular echocardiographic parameters ( $p > 0.05$ ) was noted. Peak left atrial systolic strain improved at six months ( $18.7 \pm 7.7$  vs  $23.6 \pm 8.5\%$ ,  $p = 0.02$ ).

**Conclusion:** This preliminary analysis suggests that combination anti-remodelling therapy may be beneficial for HF secondary to CRMR. We had no HF-related admissions or deaths, and no deterioration in echocardiographic parameters of ventricular size and function.

**Keywords:** heart failure, mitral regurgitation, combination therapy

Submitted 5/6/16, accepted 7/12/16

*Cardiovasc J Afr* 2017; 28: 280–284

www.cvja.co.za

DOI: 10.5830/CVJA-2016-095

For patients with valvular disease, direct pressure or volume overload results in cardiac remodelling and eventually heart failure (HF).<sup>1–3</sup> Changes in neuro-hormonal signalling and genotype result in abnormal structure and function of both the

myocyte and interstitial space.<sup>2,4</sup> In chronic mitral regurgitation (MR), the persistent volume overload of the left atrium and ventricle, after a period of compensation, results in myocardial dysfunction through these mechanisms.<sup>5</sup> This eventually culminates in atrial fibrillation, HF and death if left untreated.<sup>6</sup>

At present, surgery is the mainstay of therapy for patients with symptomatic severe MR and markers of left ventricular (LV) systolic dysfunction.<sup>7</sup> Surgery is associated with non-negligible morbidity and mortality rates, even in established centres, especially in patients with LV dysfunction and high New York Heart Association (NYHA) functional class.<sup>8,9</sup>

The use of medical therapy for chronic MR has been largely non-conclusive and controversial.<sup>10</sup> Most were small studies involving angiotensin converting enzyme (ACE) inhibitors and beta-blockers in degenerative MR.<sup>10,12</sup> Guidelines on valvular heart disease recommend medical therapy for HF (ejection fraction  $< 50\%$ ) in chronic MR (class IIa, level of evidence B).<sup>7</sup>

No study has systematically looked at the effects of combination anti-remodelling therapy (ACE inhibitors, beta-blockers, aldosterone receptor antagonist) in HF secondary to MR. There is proven mortality and morbidity benefit of combination anti-remodelling therapy in systolic HF as a result of ischaemia and cardiomyopathy.<sup>13–15</sup>

We hypothesised that a similar benefit may be derived in HF secondary to CRMR. This could potentially offer an alternative option to these patients who are at high risk for surgery or are not inclined to undergo surgical intervention. Furthermore, the benefit of anti-remodelling therapy may be extended to asymptomatic patients with significant MR to prevent disease progression and delay the time to surgery. We therefore aimed to study the effect of anti-remodelling therapy, including ACE inhibitors and beta-blockers, in terms of clinical outcome, and traditional as well as newer echocardiographic parameters, such as two-dimensional strain in patients with severe CRMR who presented with HF.

### Methods

This prospective, observational sub-study formed part of a larger study on CRMR at the Chris Hani Baragwanath Academic Hospital. Patients were enrolled between January and December 2014. The study was approved by the University of the Witwatersrand ethics committee (M140114). All patients were screened and those deemed to have severe CRMR and presented with HF were referred for possible inclusion in the study.

**Division of Cardiology, Chris Hani Baragwanath Academic Hospital and University of the Witwatersrand, Johannesburg, South Africa**

Ruchika Meel, PhD, ruchikameel@gmail.com

Ferande Peters, MD

Elena Libhaber, PhD

Mohammed R Essop, MD

HF was diagnosed as per the ACCF/AHA and ESC guideline definition.<sup>15,16</sup> The assessment of HF was made based on a combination of the patient’s history, clinical signs as well as available clinical records. A total of 66 patients with presumed CRMR underwent clinical evaluation, resting electrocardiogram and detailed echocardiographic assessment according to a predetermined protocol.

The inclusion criteria were as follows: patients aged 18 years or older with echocardiographic features of severe CRMR; symptomatic (NYHA II–III); left ventricular ejection fraction ≤ 60%; refusing or awaiting surgery; and on medical therapy [ACE inhibitors, angiotensin receptor blockers (ARBs), beta-blockers or aldosterone receptor antagonist] for HF.

Patients were excluded if they had significant aortic valve disease, concurrent mitral stenosis (MS) with a valve area of less than 2.0 cm<sup>2</sup>, documented ischaemic heart disease, pre-existing non-valvular cardiomyopathy, prior cardiac surgery, congenital or pericardial disease, pregnancy, severe systemic disorders such as renal failure, uncontrolled hypertension (systolic blood pressure > 140 mmHg and diastolic blood pressure > 90 mmHg) on medication, or severe anaemia (haemoglobin < 10 g/dl).

Thirty-five patients were excluded due to the following: anaemia, renal dysfunction, mild or moderate MR, MR of non-rheumatic aetiology and inadequate image quality. The final sample included 31 patients. Most HF trials conducted with anti-remodelling agents required a minimum duration of three months to demonstrate benefit.<sup>17</sup> We therefore followed up patients in this study for a period of six months.

All the patients included in the sub-study were receiving some form of medical therapy for HF. All were on the minimum dose of their respective HF medications and were up titrated at three months where indicated, based on symptoms, blood pressure, and urea and creatinine levels.

All patients enrolled in this study were on a combination of at least one anti-remodelling agent in addition to a diuretic for at least one week. Therapy comprised beta-blockers (atenolol, carvedilol), ACE inhibitors/ARBs (enalapril, perindopril, telmisartan) and an aldosterone receptor antagonist (spironolactone), in addition to digitalis and diuretics. Medication was initiated at the discretion of the treating physician. All medications were either down titrated or withdrawn, or substituted on follow-up visits if side effects were reported.

Patients were followed up at one, three and six months. At one and six months, a full clinical assessment was done, including the Minnesota HF questionnaire and six-minute walk test. The dose of the medication was titrated at one month and full titration was achieved at three months by the treating physician.

Transthoracic echocardiography was performed on all patients in the left lateral position by experienced sonographers using a S5-1 transducer on a Philips iE33 system (Amsterdam, the Netherlands). The images were obtained according to a standardised protocol at baseline and at the six-month follow up. The data were transferred and analysed offline using the Xcelera workstation (Philips). Echocardiographic measurements were done by the researcher at baseline and the follow-up measurements were done by an experienced sonographer who was blinded to the initial results.

For two-dimensional and Doppler quantification, all linear and volumetric chamber measurements were performed according to the American Society of Echocardiography (ASE)

chamber guidelines at baseline and at six months.<sup>18</sup> Measurements relating to LV diastolic function were performed in accordance with the ASE guidelines on diastolic function and included pulse-wave Doppler at the mitral tips and tissue Doppler of both medial and lateral mitral annuli at baseline and at six months.<sup>19</sup> Measurements relating to the right ventricle were based on the ASE guidelines on the right ventricle.<sup>20</sup>

MR was considered rheumatic in aetiology when the morphology of the valve satisfied the World Heart Federation (WHF) criteria for the diagnosis of chronic rheumatic heart disease.<sup>21</sup> MR severity was assessed using qualitative, semi-quantitative and quantitative methods (integrated approach) as per the ASE valvular regurgitation guideline.<sup>22,23</sup> In equivocal cases, the echocardiographic data were integrated with the clinical evaluation by an experienced cardiologist to distinguish moderate from severe MR.

For speckle tracking echocardiography, left atrial peak systolic strain and left and right ventricular peak systolic strain were measured as previously described.<sup>24-30</sup>

### Statistical analysis

Statistical analysis was performed with Statistica (version 12.5, series 0414 for Windows). Continuous variables are expressed as mean ± SD or median (IQR). Paired Student’s *t*-test or Wilcoxon’s matched-pairs test were used to compare continuous variables. Categorical variables are expressed as percentages. A *p*-value of < 0.05 was recognised as statistically significant.

### Results

The baseline clinical characteristics are summarised in Table 1. There was no change in systolic and diastolic blood pressure or heart rate from baseline to six months [125 ± 12.6 vs 120.1 ± 10.2 mmHg, *p* = 0.09; 76.2 ± 12.2 vs 74.2 ± 11.02 mmHg, *p* = 0.5; 71.5 (70–81) vs 71.0 (61–80) beats/min, *p* = 0.43, respectively]. The median Minnesota HF score at the start and the end of treatment at six months was 34 (18–61) and 32.5 (13–48), respectively (*p* = 0.3). There was no difference in the six-minute walk test at the onset of treatment and at six months (265.5 ± 103.0 vs 275.4 ± 71 m, *p* = 0.6).

None of the patients were hospitalised for HF and all were alive at six months. Baseline and maximum therapeutic doses of

| Variable                             | Number = 31  |
|--------------------------------------|--------------|
| Age (years)                          | 50.7 ± 8.5   |
| Gender (female/male)                 | 29/2         |
| Systolic blood pressure (mmHg)       | 125 ± 12.6   |
| Diastolic blood pressure (mmHg)      | 76.2 ± 12.2  |
| Heart rate (beats/min)               | 71.5 (70–81) |
| Body surface area (m <sup>2</sup> )  | 1.73 ± 0.16  |
| Body mass index (kg/m <sup>2</sup> ) | 28.1 ± 6.1   |
| NYHA class II–III (%)                | 31 (100)     |
| Hypertension (%)                     | 29 (93)      |
| HIV (%)                              | 7 (23)       |
| Atrial fibrillation (%)              | 2 (6.4)      |

Data are presented as median (interquartile range), mean ± SD or %.  
 HIV, human immunodeficiency virus; NYHA, New York Heart Association functional class.

their respective medications are summarised in Table 2. There was no worsening of left and right ventricular echocardiographic indices at baseline and at six months of therapy (Table 3).

Based on the integrated assessment (qualitative and quantitative parameters), MR severity did not change at the end of six months. No change in quantitative parameters of MR assessment was noted at the end of six months [(vena cava width:  $6.5 \pm 1.9$  vs  $6.0 \pm 1.6$  mm,  $p = 0.2$ ; regurgitant fraction:  $31.7$  (18.9–57.7) vs  $29.2\%$  (15.7–53.5),  $p = 0.2$ )].

Left atrial peak systolic strain increased at six months ( $18.7 \pm 7.7$  vs  $23.6 \pm 8.5\%$ ,  $p = 0.02$ ). However, no change in right and left ventricular peak systolic strain was noted at the end of combination therapy ( $-15.6 \pm 5.0$  vs  $-16.4 \pm 5.9\%$ ,  $p = 0.56$ ;  $-13.9 \pm 4.3$  vs  $-15 \pm 4.0\%$ ,  $p = 0.28$ , respectively).

## Discussion

The main findings of this study were that patients with rheumatic MR and HF who were treated with optimal medical therapy had good short-term clinical outcomes. There was no deterioration in echocardiographic parameters of cardiac performance, and there was an improvement in left atrial peak systolic strain.

Some older, pre-echocardiographic studies on rheumatic heart disease in Western populations demonstrated variable natural histories, ranging from CRMR being a benign lesion with a normal life expectancy, to it being a severe, progressive and ultimately fatal disease.<sup>31–33</sup> Natural history studies in degenerative MR, with follow up ranging from seven months to 10 years, have shown increased risk of sudden cardiac death and increased postoperative morbidity and mortality rates in the presence of severe MR symptoms, arrhythmias, left ventricular end-systolic dimensions (LVESD)  $\geq 45$  mm and ejection fraction (EF)  $\leq 60\%$ .<sup>8,34–39</sup> These studies, primarily pertaining to degenerative, significant MR, evaluated symptomatic and asymptomatic patients. Most of them concluded that with conservative management (medical therapy), outcomes were worse regarding cardiac death, progression to worsening NYHA functional class, left ventricular dysfunction, HF, atrial fibrillation and pulmonary hypertension.

Munoz *et al.*<sup>40</sup> compared 29 patients with MR on medical therapy alone to 45 patients who underwent mitral valve replacement. They found at five-year follow up, a lower survival rate, faster progression to higher NYHA class, and more complications such as HF and atrial fibrillation in the medical therapy group.<sup>40</sup> The main shortcomings of all these

studies are the inclusion of mostly asymptomatic patients with significant MR, and the medication and dosages used were not systematically documented.

The subset of patients we followed up had mostly stage D heart failure due to organic valvular heart disease. They were on varied combination anti-remodelling therapy as part of their management. This provided us with the opportunity of observing this subgroup. The lack of change in left and right ventricular structural and functional indices may possibly be explained by the short duration of follow up, the disease-stabilising effect of anti-remodelling therapy, and/or the relatively younger age of our patients compared to degenerative MR patients. A lack of difference in MR severity, even after controlling the systolic blood pressure in our study, may be explained by the small effect of change in pressure gradient on regurgitant volume, static left ventricular volumes, and the rheumatic nature of the disease, whereby the orifice is fixed and not dynamic, as in degenerative MR.<sup>5,12,41</sup>

There was no change in left and right ventricular longitudinal strain parameters in our study and this may be attributed to the short duration of follow up. The reason for marked improvement in left atrial peak systolic strain may be that the left atrium remodels and recovers earlier than the ventricles after an injury, as shown by Therkelsen *et al.*<sup>42</sup> Additionally, left atrial reverse remodelling has been known to occur independently of left ventricular reverse remodelling, due to the direct effect of drugs that inhibit the renin–angiotensin–aldosterone system (RAAS).<sup>4</sup> Also, left atrial strain may be a more sensitive marker for detecting reverse remodelling than left atrial volumes, as noted in this study.

**Table 2. Comparison between baseline and maximum medication dose of the study patients**

| Medication     | Number (%) | Baseline dose (mg) | Dose (mg) at six months | p-value |
|----------------|------------|--------------------|-------------------------|---------|
| Furosemide     | 30 (97)    | 75 $\pm$ 25.9      | 78.3 $\pm$ 34.9         | 0.67    |
| Nifedipine XL  | 9 (29)     | 34.4 $\pm$ 21.8    | 47.7 $\pm$ 24.3         | 0.23    |
| Digoxin        | 7 (23)     | 0.125              | 0.125                   | 1.0     |
| Enalapril      | 11 (35)    | 10 (2.5–20)        | 20 (10–20)              | 0.17    |
| Perindopril    | 11 (35)    | 2.9 $\pm$ 1        | 4 $\pm$ 1.7             | 0.003   |
| Carvedilol     | 29 (94)    | 12.5 (3.125–12.5)  | 50 (37.5–50)            | < 0.001 |
| Spironolactone | 28 (90)    | 25 (12.5–25)       | 50 (50–75)              | 0.001   |

Data are presented as median (interquartile range), mean  $\pm$  SD or %. Two patients were on telmisartan (40 mg at baseline and six months), and one was on atenolol (12.5 mg up-titrated to 25 mg at six months).

**Table 3. Left and right ventricular echocardiographic parameters at baseline and six months of medical therapy**

| Variable                               | Baseline (n = 31) | Six months of therapy (n = 31) | p-value |
|--|-------------------|--------------------------------|---------|
| Left ventricular indices               |                   |                                |         |
| LVEDD (mm)                             | 55.5 $\pm$ 8.4    | 55.1 $\pm$ 8.0                 | 0.8     |
| LVESD (mm)                             | 42.6 $\pm$ 9.4    | 40.7 $\pm$ 9.5                 | 0.43    |
| EDVi (ml/m <sup>2</sup> ) <sup>†</sup> | 81.8 (68.9–98.1)  | 79.1 (64.5–99.3)               | 0.6     |
| ESVi (ml/m <sup>2</sup> ) <sup>†</sup> | 45.4 $\pm$ 17.8   | 42.8 $\pm$ 15.8                | 0.5     |
| Ejection fraction (%)                  | 46.9 $\pm$ 8.7    | 50.4 $\pm$ 10.1                | 0.1     |
| E wave (cm/s)                          | 113.2 $\pm$ 47.2  | 112.9 $\pm$ 42.1               | 0.9     |
| A wave (cm/s)                          | 102.0 $\pm$ 26.5  | 99.4 $\pm$ 28                  | 0.7     |
| E/A wave (ratio)                       | 1.0 $\pm$ 0.4     | 1.1 $\pm$ 0.4                  | 0.3     |
| E' medial (cm/s)                       | 6.6 (4.5–8.2)     | 5.9 (4.7–7.8)                  | 0.2     |
| A' medial (cm/s)                       | 6.7 (5.1–8.2)     | 7.1 (5.9–8.3)                  | 0.5     |
| Medial E/E' (ratio)                    | 18.5 $\pm$ 9.5    | 18.9 $\pm$ 9.7                 | 0.8     |
| Medial S' (cm/s)                       | 6.1 $\pm$ 1.4     | 6.1 $\pm$ 1.2                  | 1.0     |
| LAVi (ml/m <sup>2</sup> ) <sup>†</sup> | 60.2 (47.1–89.4)  | 59.5 (44.2–82.4)               | 0.8     |
| Right ventricular indices              |                   |                                |         |
| RV base (mm)                           | 38.3 $\pm$ 6.25   | 35.8 $\pm$ 8.8                 | 0.2     |
| TAPSE (mm)                             | 20.5 $\pm$ 2.9    | 20.6 $\pm$ 2.9                 | 0.9     |
| RV S' (cm/s)                           | 11.1 $\pm$ 2.7    | 11.6 $\pm$ 2.5                 | 0.45    |
| RAVi (ml/m <sup>2</sup> ) <sup>†</sup> | 26.5 (21.7–32)    | 24.7 (7.4–33.8)                | 0.6     |
| PASP (mmHg)                            | 33.2 $\pm$ 12.4   | 31.4 $\pm$ 11.5                | 0.5     |

Data are presented as median (interquartile range), mean  $\pm$  SD or %. <sup>†</sup>Values are indexed to body surface area. EDVi, end-diastolic volume index; ESVi, end-systolic volume index; LAVi, left atrial volume index; EDD, end-diastolic diameter; ESD, end-systolic diameter; LV, left ventricle; PASP, pulmonary artery systolic pressure; RAVi, right atrial volume index; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion.

There are a number of studies that have evaluated the effects of individual drugs in degenerative MR. Most of these involved beta-blockers or vasodilators.<sup>12,43</sup> The results from these mostly small, non-randomised trials were inconclusive.<sup>10,44</sup> The effect of aldosterone receptor antagonists has not been evaluated in organic MR in humans. Additionally, no trial has systematically explored the effects of combination therapy (with or without HF), secondary to CRMR.

In our study, lack of benefit from individual agents may have been due to incomplete blockade of the sympathetic nervous system (SNS) or the RAAS. An example would be that of aldosterone escape during prolonged ACE inhibitor therapy.<sup>45</sup> Other possibilities include activation of the kallikrein-kinin system due to an increase in bradykinin, which in turn activates matrix metalloproteinases, resulting in collagen loss, a process that may be exacerbated by the inhibition of angiotensin II by ACE inhibitors.<sup>46</sup>

These drugs in combination have synergistic action; for example the combination of an ACE inhibitor, beta-blocker and aldosterone receptor antagonist suppresses myocardial fibrosis in systolic heart failure.<sup>3</sup> Therefore, combination therapy with drugs that block the SNS and RAAS systems may be the answer. Most of our patients were on a combination of carvedilol, spironolactone and an ACE inhibitor. However, their effect on left ventricular function and rheumatic MR severity remains questionable.

All the patients however remained stable on combined medical therapy and none was hospitalised for HF or died during the six months of follow up. This is a relevant finding as more than 50% of patients with all-cause systolic HF are re-hospitalised within six months of HF assessment.<sup>47</sup> The lack of sudden cardiac death and HF-related deaths in this study may be attributed to medical treatment, or perhaps chance, due to the small sample size. Combined medical therapy may serve to stabilise the disease process, probably via neuro-hormonal modulation (likely the most important compensatory and deleterious mechanism in MR).<sup>48</sup> Combination HF therapy may therefore serve as a bridge to surgery, given the long delays due to resource limitations, or as a substitute for surgery where patients decline surgery or have a high surgical risk due to severe ventricular dysfunction.

There were several limitations to this observational study. We had no control arm, there was a varied combination of medications, the exact duration of therapy at baseline was not clear due to incomplete records, the study subjects and the researchers were not blinded to the treatment, it was a small sample size, and the follow-up period was short.

## Conclusion

We have shown that combination anti-remodelling medical therapy in CRMR may be beneficial to prevent hospitalisation for HF and death. It may have a stabilising effect on HF secondary to chronic rheumatic MR. Further larger studies are needed to test the effect of combination therapy on chronic organic MR.

Dr Meel was the recipient of the Carnegie PhD Fellowship award (Carnegie Corporation Grant No. b8749.r01).

## References

- Hilfiker-Kleiner D, Landmesser U, Drexler H. Molecular mechanisms in heart failure focus on cardiac hypertrophy, inflammation, angiogenesis, and apoptosis. *J Am Coll Cardiol* 2006; **48**: A56–66. doi:10.1016/j.jacc.2006.07.007.
- Cohn J, Ferrari R, Sharpe N. Cardiac remodelling – concepts and clinical implications: A consensus paper from an international forum on cardiac remodeling. *J Am Coll Cardiol* 2000; **35**: 569–582. doi:10.1016/S0735-1097(99)00630-0. PMID: 10716457.
- Bonow R, Mann D, Zipes D, Libby P. Pathophysiology of heart failure. In: Bonow R, Mann D, Zipes D, Libby P (eds). Braunwald's Heart Disease. 9th edn. Philadelphia: Elsevier Saunders: 487–504.
- Casaclang-Verzosa G, Gersh B, Tsang T. Structural and functional remodeling of the left atrium. Clinical and therapeutic implications for atrial fibrillation. *J Am Coll Cardiol* 2008; **51**: 1–11. doi: 10.1016/j.jacc.2007.09.026. PMID: 18174029.
- Gaasch WH, Meyer TE. Left ventricular response to mitral regurgitation: implications for management. *Circulation* 2008; **118**: 2298–2303. doi: 10.1161/CIRCULATIONAHA.107.755942. PMID: 19029478.
- Borg A, Pearce K, Williams S, et al. Left atrial function and deformation in chronic primary mitral regurgitation. *Eur J Echocardiogr* 2009; **10**: 833–840. doi:10.1093/ejehocardiography/jep085.
- Nishimura R, Otto C, Bonow R, et al. 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 practice guidelines. *J Am Coll Cardiol* 2014; **63**: e57–e185. doi: 10.1016/j.jacc.2014.02.536. PMID: 24603191.
- Enriquez-Sarano M, Schaff HV, Orszulak TA, et al. Valve repair improves the outcome of surgery for mitral regurgitation. A multivariate analysis. *Circulation* 1995; **91**: 1022–1028. PMID: 7850937.
- Tribouilloy CM, Enriquez-Sarano M, Schaff HV, et al. Impact of preoperative symptoms on survival after surgical correction of organic mitral regurgitation: rationale for optimizing surgical indications. *Circulation* 1999; **99**: 400–405. PMID: 9918527.
- Carabello B. The current therapy for mitral regurgitation. *J Am Coll Cardiol* 2008; **52**: 319–326. doi: 10.1016/j.jacc.2008.02.084. PMID: 18652937.
- Ahmed M, Aban I, Lloyd S, et al. A randomized controlled phase IIb trial of beta1-receptor blockade for chronic degenerative mitral regurgitation. *J Am Coll Cardiol* 2012; **60**: 833–838. doi: 10.1016/j.jacc.2012.04.029. PMID: 22818065.
- Evangelista A. Usefulness of vasodilator therapy in regurgitant valvular diseases. *Rev Esp Cardiol* 2007; **60**: 223–227. PMID: 17394865.
- Cicoira M, Zanolla L, Rossi A, et al. Long-term, dose-dependent effects of spironolactone on left ventricular function and exercise tolerance in patients with chronic heart failure. *J Am Coll Cardiol* 2002; **40**: 304–310. PMID: 12106936.
- Merlo M, Pyxaras S, Pinamonti B, et al. Prevalence and prognostic significance of left ventricular reverse remodeling in dilated cardiomyopathy receiving tailored medical treatment. *J Am Coll Cardiol* 2011; **57**: 1468–1476. doi: 10.1016/j.jacc.2010.11.030. PMID: 21435516.
- Yancy C, Jessup M, Bozkurt B, et al. Guideline for the management of heart failure. A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *Circulation* 2013; **128**: e240–e327. doi: 10.1161/CIR.0b013e31829e8776. PMID: 23741058.
- McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012; **14**: 803–869.



- doi: 10.1093/eurjhf/hfs105. PMID: 22828712.
17. Bangalore S, Kumar S, Messerli FH. When conventional heart failure therapy is not enough: angiotensin receptor blocker, direct renin inhibitor, or aldosterone antagonist? *Congest Heart Fail* 2013; **19**: 107–115. doi: 10.1111/chf.12011. PMID: 23241032.
  18. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; **28**: 1–39.e14. doi:10.1016/j.echo.2014.10.003. PMID: 25559473.
  19. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr* 2009; **10**: 165–193. doi: 10.1093/ejehocardiography/jep007. PMID: 19270053.
  20. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: A report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; **23**: 685–713. doi: 10.1016/j.echo.2010.05.010. PMID: 20620859.
  21. Reményi B, Wilson N, Steer A, et al. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease – an evidence-based guideline. *Nat Rev Cardiol* 2012; **28**: 297–309. doi: 10.1038/nrcardio.2012.7. PMID: 22371105.
  22. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Scientific document committee of the European Association of Cardiovascular Imaging. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2013; **14**: 611–644. doi: 10.1093/ehjci/jet105. PMID: 23733442.
  23. Lancellotti P, Moura L, Pierard LA, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). *Eur J Echocardiogr* 2010; **11**: 307–332. doi: 10.1093/ejehocardiography/jeq031.
  24. Cameli M, Caputo M, Mondillo S, et al. Feasibility and reference values of left atrial longitudinal strain imaging by two-dimensional speckle tracking. *Cardiovasc Ultrasound* 2009; **7**: 6. doi: 10.1186/1476-7120-7-6. PMID: 19200402.
  25. Vianna-Pinton R, Moreno C, Baxter C, et al. Two-dimensional speckle-tracking echocardiography of the left atrium: feasibility and regional contraction and relaxation differences in normal subjects. *J Am Soc Echocardiogr* 2009; **22**: 299–305. doi: 10.1016/j.echo.2008.12.017. PMID: 19258177.
  26. Younan H. Role of two dimensional strain and strain rate imaging in assessment of left ventricular systolic function in patients with rheumatic mitral stenosis and normal ejection fraction. *Egyptian Heart J* 2015; **67**: 193–198. doi:10.1016/j.ehj.2014.07.003.
  27. Marciniak A, Claus P, Sutherland G, et al. Changes in systolic left ventricular function in isolated mitral regurgitation. Strain rate imaging study. *Eur Heart J* 2007; **28**: 2627–2636. PMID: 17526904.
  28. Kocabay G, Muraru D, Peluso D, et al. Normal left ventricular mechanics by two-dimensional speckle-tracking echocardiography. Reference values in healthy adults. *Rev Esp Cardiol* 2014; **67**: 651–658. doi.org/10.1016/j.rec.2013.12.009.
  29. Kumar V, Jose V, Pati P, et al. Assessment of right ventricular strain and strain rate in patients with severe mitral stenosis before and after balloon mitral valvuloplasty. *Indian Heart J* 2014; **16**: 176–182. doi.org/10.1016/j.ihj.2014.02.012.
  30. Todaro M, Romano G, Carerj S, et al. Right ventricular free wall strain: a predictor of successful left ventricular assist device implantation. *Texas Heart Inst J* 2015; **42**: 87–89. doi.org/10.14503/THIJ-14-4111.
  31. Ellis LB, Ramirez A. The clinical course of patients with severe ‘rheumatic’ mitral insufficiency. *Am Heart J* 1969; **78**: 406–418. PMID: 4241075.
  32. Jhaveri S, Czoniczer G, Reider RB. Relatively benign ‘pure’ mitral regurgitation of rheumatic origin. A study of seventy-four adult patients. *Circulation* 1960; **22**: 39–48. PMID: 14407272.
  33. Wilson MG, Lim WN. The natural history of rheumatic heart disease in the third, fourth, and fifth decades of life. Prognosis with special reference to survivorship. *Circulation* 1957; **16**: 700–712. PMID: 13473042.
  34. Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, et al. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. *N Engl J Med* 2005; **352**: 875–883. PMID: 15745978.
  35. Rosenhek R, Rader F, Klaar U, et al. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. *Circulation* 2006; **113**: 2238–2244. PMID: 16651470.
  36. Tribouilloy C, Grigioni F, Avierinos JF, et al. Survival implication of left ventricular end-systolic diameter in mitral regurgitation due to flail leaflets a long-term follow-up multicenter study. *J Am Coll Cardiol* 2009; **54**: 1961–1968. doi: 10.1016/j.jacc.2009.06.047. PMID: 19909877.
  37. Grigioni F, Enriquez-Sarano M, Ling LH, et al. Sudden death in mitral regurgitation due to flail leaflet. *J Am Coll Cardiol* 1999; **34**: 2078–2085. PMID: 10588227.
  38. Kligfield P, Hochreiter C, Niles N, et al. Relation of sudden death in pure mitral regurgitation, with and without mitral valve prolapse, to repetitive ventricular arrhythmias and right and left ventricular ejection fractions. *Am J Cardiol* 1987; **60**: 397–399. PMID: 3618505.
  39. Grigioni F, Tribouilloy C, Avierinos JF, et al. Outcomes in mitral regurgitation due to flail leaflets a multicenter European study. *J Am Coll Cardiol Cardiovasc Imaging* 2008; **1**: 133–141. doi: 10.1016/j.jcmg.2007.12.005. PMID: 19356418.
  40. Muñoz S, Gallardo J, Diaz-Gorriñ JR, et al. Influence of surgery on the natural history of rheumatic mitral and aortic valve disease. *Am J Cardiol* 1975; **35**: 234–242. PMID: 1119383.
  41. Jeang MK, Petrovich LJ, Adyanthaya AV, et al. Effects of isosorbide dinitrate on rheumatic and non-rheumatic mitral regurgitation. *Texas Heart Inst J* 1986; **13**: 453–457. PMID: 15227354.
  42. Therkelsen SK, Groenning BA, Svendsen JH, et al. Atrial and ventricular volume and function evaluated by magnetic resonance imaging in patients with persistent atrial fibrillation before and after cardioversion. *Am J Cardiol* 2006; **97**: 1213–1219. PMID: 16616028.
  43. Carabello B. Beta-blockade for mitral regurgitation. Could the management of valvular heart disease actually be moving into the 21st century? *J Am Coll Cardiol* 2012; **60**: 839–840. PMID: 22818062.
  44. Borer J. Mitral regurgitation: has another ‘magic bullet’ bitten the dust? *Circ Heart Fail* 2013; **6**: 624–626. doi:10.1161/CIRCHEARTFAILURE.113.000409. PMID: 23861504.
  45. Opie L, Gersh B. Inhibitors of the renin–angiotensin–aldosterone system. In: Opie L, Gersh B (eds). *Drugs for the Heart*. 8th edn. Philadelphia: Elsevier Saunders: 119–168.
  46. Wei C, Chen Y, Powell L, et al. Cardiac kallikrein–kinin system is upregulated in chronic volume overload and mediates an inflammatory induced collagen loss. *PLoS One* 2012; **7**. doi: 10.1371/journal.pone.0040110. PMID: 22768235.
  47. Desai AS, Stevenson LW. Rehospitalization for heart failure: predict or prevent? *Circulation* 2012; **126**: 501–506. doi: 10.1161/CIRCULATIONAHA.112.125435. PMID: 22825412.
  48. Tsutsui H, Spinale FG, Nagatsu M, et al. Effects of chronic beta-adrenergic blockade on the left ventricular and cardiocyte abnormalities of chronic canine mitral regurgitation. *J Clin Invest* 1994; **93**: 2639–2648. PMID: 7911128.