Targeting Reverse Remodeling in Sudanese Patients with Dilated Cardiomyopathy Receiving Tailored Medical Therapy: 6 Months Outcome

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DOI: 10.29322/IJSRP.14.07.2024.p15217

Paper Received Date: 25th July 2024
Paper Acceptance Date: 25th August 2024
Paper Publication Date: 30th August 2024

Abstract:

Background: After removing any possible cause of LV dysfunction, if detectable at diagnosis, and treatment optimization, myocardial remodeling can be reversed, and this will lead to better cardiac function and consequent better prognosis. Studies showed that is reasonable to evaluate patients 3 to 9 months after implementation of optimal medical treatment in order to identify candidates for. After addressing any possible causes of LV dysfunction, if detectable at diagnosis, and optimizing treatment, myocardial remodeling can be reversed, resulting in improved heart function and a better prognosis. According to studies, it is fair to examine patients 3 to 9 months after implementing optimal medical treatment in order to identify candidates for next step after medical therapy. **Aim:** This research aimed to measure the frequency in detection of early left ventricular reverse remodeling (LVRR) amongst non-ischemic cardiomyopathy patients in the Republic of the Sudan, who received optimized medical therapy in a duration of 6 months with the aim to determine the clinical predictors of RR & to study whether this is a sufficient duration for detecting improvement in left ventricular function. **Methods**: a retrospective study conducted among 69 patients of non-ischemic DCM in Fedail Hospital & Alshaab Teaching Hospital in Khartoum state in the period from April 2019 to the end of August 2019. Patients who achieved an increase of ≥ 10LV ejection fraction (LVEF) units and LV reverse remodeling (LVRR) in the 6 months duration were compared to patients who did not improve to this level in form of demographic data, co-morbidities, symptomatology, and their echocardiography findings. **Results:** Among 69 patients, 17 (24, 6%) had reversed remodeling, 14 (20.3%) had considerable improvement in their LVEF% but not fulfilling the definition of reversed remodeling and 38 (55, 1%) showed mild or non-improvement in their LVEF%. Younger age (under 60) was significantly associated with reversed remodeling in comparison to more than 60-year age group (P< 0.05). 14 (82.3%) patients of RR group their heart failure duration was less than 2 years meanwhile non-RR group most of them were diagnosed more than 2 years, 34 (65,4%) patients. The predictors of RR in our patients were absence of atrial fibrillation & negative smoking history. Regarding the implications of RR In our patients with non-ischemic DCM, there was neither detectable severe mitral regurgitation nor intra-cardiac thrombus at the end of 6 months duration. **Conclusion & recommendations**: cardiac reversed remodeling is important treatment goal & it can be achieved in the first 6 months of follow up with fully optimized medical therapy. Our study found that 17 (24.6%) patients they developed RR while 14 (20.3%) had considerable improvement in their LVEF% but not fulfilling the definition of RR and 38 (55.1%) showed mild or non-improvement in their LVEF%. It important to stress on using echocardiography as a tool for follow up in all patients with DCM in Sudan.

DCM at a glance:

Dilated Cardiomyopathy (DCM) is a cardiac illness characterized by left ventricular (LV) or biventricular dilation and systolic dysfunction in the absence of pressure overload or coronary artery disease that would otherwise explain the observed myocardial dysfunction (1).

It is estimated that incidence and prevalence of DCM is at approximately 7/100.000 people/year and 1 in 2500 respectively in western populations, but there are marked race-related differences and geographical differences. Data indicates prevalence of DCM in Africa and Latin America to be double that of western populations (2).

DCM can be classified as genetic or non-genetic (1), with genetic causes representing 30–40% of DCMs. Transmission varies, but an autosomal dominant pattern seems more prevalent (3).

Prognosis of DCM was considered ominous previously (4). For a number of decades now, the 10- year survival rate, free from heart transplantation, has drastically improved and currently stands at approximately 85% (5). Nevertheless, the outcome of patients with DCM quite often remains unpredictable and major adverse events may, and do, occur in the first months following the diagnosis (6).

Pathophysiology of cardiac remodeling:

Cardiac remodeling in response to an inciting myocardial insult or an underlying genetic abnormality has been classically considered the hallmark of DCM. It can be defined as the result of molecular, cellular, and histological myocardial changes that determine macroscopic alterations in the size, shape, and function of the cardiac muscle (7).

Those factors that drive remodeling can be divided into two broad categories: mechanical stress and biochemical stress owing to abnormal circulating and local neurohormonal and cytokine factors. These stress signals lead to cardiomyocyte hypertrophy, apoptosis, and a reduction in contractile strength, with profound effects on gene expression, protein function, signaling pathways, metabolic processes, and electrophysiological properties (8).

Clinical and experimental evidence suggests that the renin–angiotensin–aldosterone system and sympathetic nervous system play an important role in the process (9).

Cardiac dilation is identified as an important marker of poor prognosis. Conversely, its reversal is associated with improved prognosis (9).

Functional mitral regurgitation (MR) is a common finding in patients with DCM resulting from dilation of the annulo-ventricular apparatus, the increased sphericity of ventricular geometry and apico-lateral displacement of the papillary muscles (10,11). MR exacerbates the volume overload of the already dilated left ventricle (LV), leading to progressive ventricular and annular dilation, heart failure deterioration and predicts a poor survival. Functional MR is a frequent finding in patients with DCM and its severity is associated with prognosis (12,13).

DCM: Treatment and outcome:

The classical medical management of DCM is based on treatment with Angiotensin-Converting Enzyme (ACE) inhibitors/angiotensin receptor blockers, beta-blockers and mineralocorticoid receptor antagonists (9).

The systematic implementation of evidence based medical and device therapies that promote Left Ventricular Reverse Remodeling (LVRR), defined as an improvement in Left Ventricular Ejection Fraction (LVEF), and a reduction in left ventricular dimension.

Therapy-induced reverse remodeling has been recently recognized as an important prognostic tool in the management of patients with DCM (14,15).

Among pharmacological therapies, beta-adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and aldosterone antagonists improved cardiac function and left ventricular dimension when given separately or together (16,17).

Several studies have demonstrated that drugs or procedures, which modify ventricular remodeling, preventing or delaying cardiac dilation, are associated with improved outcomes. But not all drugs used in the treatment of HF influence cardiac remodeling (14).

ACE inhibitors, as demonstrated in the SOLVD studies, reduced the rate of cardiac dilation and, in initial forms, promoted regression in cardiac dilation (18). Studies have shown reversal of cardiac dilation in approximately 30%–60% of the cases treated with neurohormonal blockers (9).

Recent reports have suggested that reverse remodeling might be a global myocardial process involving not only left ventricle contractile function, but also mitral regurgitation, left ventricular diastolic function and the right ventricle (19).

Reverse remodeling & related important definitions:

Can take place spontaneously upon removal of the inciting cardiac insult (for instance in tachycardia induced cardiomyopathy or toxin-induced cardiomyopathy) but it is more often the result of evidence-based pharmacological and non-pharmacological therapies (20).

LVRR was defined as ‘the combined presence at mid-term follow-up of: 1) an increase in LVEF of at least 10 points or a follow-up LVEF50% (in patients with an LVEF of 45% to 49% at enrollment); and 2) a decrease in indexed left ventricular end-diastolic diameter of at least 10% or an indexed left ventricular end-diastolic diameter 33 mm/m2’ (21).

Current American College of Cardiology/American Heart Association guidelines define a cohort of “HFpEF, improved” patients as those who have LVEF>40% but who previously had LVEF#40% (22). European Society of Cardiology guidelines introduced a category called “HF with midrange EF” (HRmrEF) (LVEF 40% to 49%) but do not distinguish between patients who previously had lower LVEF and those who have never had HFrEF (14). Other investigators have defined a cohort of patients with HF with recovered EF (HFrecEF) or HF with better EF (HF better EF) as those who have LVEF 50% but with a previously documented LVEF<50% (23,24). HF with improved EF (HFiEF) has been proposed to define patients with LVEF>40% with a previously documented LVEF<35% (7).

Predicting improvement in LVEF:

It is clear is that the frequency of LVEF improvement depends on the cause of the underlying cardiomyopathy (25).

These include female sex, non-ischemic cause of HF, shorter duration of HF, and less severe adverse cardiac remodeling at initial evaluation. These factors have also been associated with super-response to CRT (26). However, although the presence of left bundle

branch block (LBBB) is also predictive of CRT response, LBBB is associated with attenuated LVEF improvement or lack of LVEF improvement with optimal medical therapy alone (26,14).

Published data exists on the influence of genetics on LVEF improvement. Activating mutations in the angiotensin-converting enzyme (ACE) or β1-adrenergic receptor genes have been linked, in these studies, to a relatively negative LVEF response to medical therapy (27).

Implications of RR:

Following improvement of LVEF, the laboratory investigations, and functional characteristics of HFiEF patients are more favorable than those of HFrEF patients. The phenotypic improvement of individuals living with HFrEF is not necessarily reflective of complete recovery from adverse structural remodeling or remission of HF (28).

Exercise capacity of HFiEF patients also appears to be reduced relative to healthy controls, with average peak oxygen consumption reported as 17 to 18 ml/kg/min (53% predicted) (29). Finally, although HFiEF patients reported better quality of life than HFrEF patients, 25% to 75% still reported HF symptoms despite good adherence to medical therapy (6,23,30).

A finding suggesting that it is the RR itself that leads to increased survival (31). Hospitalizations are also decreased in HFiEF patients compared with patients with HFrEF (9,32). However, overall survival is still worse than in healthy controls (33).

Mechanisms of LVEF Improvement:

The link between adherence to HF therapy and LVEF improvement suggests that the pathways targeted by HF therapies may provide mechanistic insight into the process of LVEF improvement. Up regulated angiotensin II signaling, similar to the neurohormonal activation seen in HFrEF patients, leads to deleterious myocyte hypertrophy mediated by transforming growth factor-b and endothelin-1 (34). ACE inhibitors down-regulate this pathway by suppressing fibroblast signaling and collagen deposition (35). ACE inhibitors and angiotensin receptor blockers (ARBs) also reduce the effect of β-adrenergic stimulation by enhancing myocardial nitric oxide production (36).

Stimulation of adrenergic receptors results in myocyte hypertrophy and, eventually, the development of HF, mediated through G-protein–coupled receptor pathways (37). β-blockers function in the restoration of normal G-protein–coupled receptor function and improve contractility of the heart (38). Furthermore, they restore normal calcium signaling via normalizing ryanodine receptor function, resulting in even increased contractility (39).

Outcome After RR:

Natural history studies have shown that HFiEF patients remain at some risk of developing HFrEF again (6). Just as more severe LV remodeling is associated with lower rates of LVEF improvement, HFiEF patients with larger LV size appear to be at higher risk of future deterioration in LVEF (12).

Interestingly, only about 10% of DCM patients showed persistent apparent healing at long term (10 years) and the vast majority of them experienced a recurrence of left ventricular dysfunction in the very long term, showing that the observed healing was only apparent and that true myocardial recovery is at most a rare event in DCM patients (40).

Problem Statement:

LV remodeling is a major pathogenic process in DCM patients, cause of progression and a predictor of prognosis (41).

Rationale/Justification:

Targeting the remodeling process to prevent it or even revert it, therefore RR constitutes a primary therapeutic goal. Moreover, the identification of reverse remodeling in Sudanese Patients with non-ischemic DCM of crucial importance as identification of patients with a likelihood of cardiac improvement has important implications for management strategies.

DCM, Medical Treatment and Outcome:

E. Hoshikawa et al. concluded that DCM does not represent an irreversible progressive pathway of myocardial failure but it is rather a dynamic disease with non-linear progression (11).

Arad M et al. found that Contemporary therapies led to an improvement in the condition of a considerable number of DCM patients. A period of close observation while optimizing medical therapy should be considered before deciding on invasive procedures (42).

RR Occurrence & Its Prognostic Value:

Verhaert and colleagues reported that reverse remodeling can take place spontaneously upon removal of the inciting cardiac insult (for instance in tachycardia induced cardiomyopathy or toxin-induced cardiomyopathy) but it is more often the result of evidence-based pharmacological and non-pharmacological therapies (43).

Cardiac remodeling improvement has also been observed (44).

It has been shown that β-blockers promote a more intense reversal of cardiac dilation when compared to ACE inhibitors (45).

At follow-up, Cioffi and colleagues (2) demonstrated that patients with reverse cardiac remodeling had lower mortality (3%) compared with those who did not present reversal (22%). In the V-HeFT I study, mortality in the first year of follow-up for patients who had a reduction in ejection fraction greater than 6 units, an alteration in ejection fraction ranging between −5 and 5 units, and those who had an increase in ejection fraction greater than five units was 29%, 16% and 6%, respectively (3).

At least 1 study (46) observed that prognosis is related to the reversal of cardiac dilation.

A number of moderate-sized HFiEF cohorts have reported 5-year survival rates ranging between 80% and 90%, as opposed to 65% to 75% in individuals with HFrEF (47-49). Better findings manifest patients whose LVEF normalizes, even those who experience partial improvement in LVEF (to 41% to 49% from<35%) were found to have higher chances of survival relative to patients whose LVEF is persistently 41% to 49% (5).

Kramer and colleagues (50) observed that, in addition to the analysis of clinical trials and small group studies, reverse cardiac remodeling was assessed in meta-analysis involving 69,766 patients in 30 randomized trials, which showed a strong relationship between improved ejection fraction and reduced mortality. Overall, mortality significantly decreased by 49% in patients presenting improved ejection fraction compared with those who did not. Based on the regression analysis, a 5% increase in mean ejection fraction corresponded to a relative reduction of 14% in mortality. For each 5% absolute increase in ejection fraction, patients who presented reversals had a 4.9-fold higher chance of not dying compared with those showing no reversal. Similar results were described for the change in left ventricular volume (50).

LVRR Predictors:

In a study of outpatients over 70 years of age, Cioffi et al. observed an improvement in the ejection fraction in 36% during a mean follow-up of 17 months. Predictors for this improvement were absence of diabetes, history of hypertension, and treatment with β-blockers; treatment with β-blockers increased the chance of reversal by 3.4 times (51).

McNamara DM et al. concluded that Outcomes in ROCM are favorable but differ by race. Left ventricular end-diastolic diameter by transthoracic echo at presentation was most predictive of subsequent myocardial recovery. Myocardial recovery was more evident in women. Clinical outcomes were worse in blacks for transplant-free survival (52).
In the V-HeFT I and II studies, reverse remodeling was also observed both in the group treated with hydralazine and nitrate and that treated with enalapril. A 5 unit increase in ejection fraction was the best predictor of mortality among the studied variables (53).

Goland and colleagues, in their study, stated that patients who experienced LV improvement and LVRR in their study had lower prevalence of LBBB and a clear trend toward lower prevalence of NYHA class 3–4 (54).

In their study, Arad and colleagues stated that Familial DCM, which is a chronic deleterious process, caused by an encoded defect in a protein function, was associated with a low likelihood of recovering function (55). A recent study examined the efficacy of the drug carvedilol on early familial DCM and reported that, while no difference was found after 6 months, there was a trend towards a decrease in the LV dimensions after 40 months of therapy (56).

Acute peripartum stress (hypertensive crisis, sepsis, etc.) was found to be associated with acute heart failure associated with a transient decrease in cardiac function (57). Historically, chemotherapy-induced cardiomyopathy is associated with poor prognosis (58).

Darjie and colleagues observed that the literature documents that adrenergic activity plays an important role in ventricular remodeling, greater than that of the renin–angiotensin system, at least in the most symptomatic forms of the disease. Conversely, the adrenergic system may not be greatly stimulated in the initial phases of ventricular dysfunction because blockage of this system in asymptomatic forms of ventricular dysfunction does not result in a very significant reduction in mortality, as demonstrated in the CAPRICORN study (59).

There were no differences in response between the ACE-inhibitor and ARB treatments analyzed in the ELITE study (60). ACE-inhibitors prevent ventricular dilation and promote small increases in ejection fraction, but reduction in ventricular diameter and increase in ejection fraction are more significant with β-blockers (61).

In the treatment of HF, dosage is extremely important. Reverse remodeling is often not observed because the treatment drugs are administered at low doses. The importance of dosage can be observed in the FAST–Carvedilol study (62).

The presence of atrial fibrillation also can inhibit reverse remodeling. Restoration of sinus rhythm by catheter ablation can lead to high rates of normalization of LVEF in HFrEF patients, a phenomenon seen less frequently with rate control alone (28).

Frequency of RR & Timing:

In the last decade, several cohort studies have shown that a significant portion of patients with DCM (i.e. about 40%) can experience a reversal of this phenomenon, which is RR, and reveals average time of occurrence of RR (63).

Merlo and colleagues concluded that the best timing of evaluation remains debated. After removing any possible cause of LV dysfunction, if detectable at diagnosis, it is reasonable to evaluate patients 3 to 9 months after implementation of optimal medical treatment in order to identify candidates for ICD implant (64).

Ideally, frequency of LVEF improvement would be assessed in patients with new onset HFrEF (3).

Ikeda and colleagues concluded that reduction in LV dimensions during the first 6 months provides beneficial information for prediction of patients who showed LVRR ≥24 months (65).

In an early study, Punnoose and colleagues analyzed 358 patients from a tertiary care HF center and identified 177 patients with LVEF 40% who would conventionally have had a diagnosis of HFpEF. In that study, LV volumes were larger in HFiEF patients than in HFpEF patients, a finding suggesting some degree of residual adverse remodeling despite improvement of LVEF (30).

Givertz and colleagues documented rates of LVEF improvement when considering causes of cardiomyopathy such as tachycardia, Takotsubo, and hyperthyroidism among patients with recent onset cardiomyopathy (30). In a tertiary care center cohort of over 1,800 patients with HF, only 10% of patients had HFiEF (23).

Similarly, 9% of patients selected for analysis from Val-HeFT (Valsartan Heart Failure Trial) went on to experience LVEF improvement to 40% during the first 12 months of follow-up (66).

Implications of RR:

Kuperstein and colleagues stated that reverse remodeling is a common finding in DCM. Reduction in the severity of functional MR is quite prevalent in patients with DCM who present with significant MR and reverse remodel during follow-up (67).

Beyond RR:

Matsumura and colleagues demonstrated the role of reverse remodeling in long-term prognosis. This study revealed that in 12 years of follow-up, all patients who had regression of cardiac dilation survived; however, those presenting increased dilation died or required transplantation (68).

There are data from small, prospective studies to support continuation of β-blocker therapy in HFiEF patients (69).

Echocardiography Findings & Functional Class:

A study reported that a smaller LVEDD at baseline was associated with higher LVEF at 6 months, independent of sex; higher NYHA functional class was associated with lower LVEF at 6 months (7).

Objectives

General Objective: To study reverse remodeling (RR) in Sudanese Non-ischemic DCM patients receiving optimal pharmacological treatment in 6 months duration.

Specific Objectives:

1- To measure the frequency of early RR among Sudanese patients with non-ischemic DCM receiving optimal pharmacological treatment in 6 months duration.
2- To determine the clinical predictors of RR in Sudanese non-ischemic DCM patients.
3- To study the sufficiency of 6 months duration for detecting improvement in left ventricular function.

Study design: This was a cross-sectional, observational, retrospective, hospital-based study that was conducted from April 2019 to the end of August 2019.

Study area: 2 hospitals located in Khartoum, Khartoum, Sudan

1- Fedail Specialized Hospital
2- Alshaab Teaching Hospital

Inclusion criteria: Adult Patients with DCM attending cardiology clinics who have initial proper assessment clinically and echocardiography profile documented in the hospital medical notes & ECHO lab computer system.

Exclusion criteria: i) Below 18 years, ii) patients with known ischemic DCM, iii) pregnant ladies

Sample size: Total coverage of all patients meeting our inclusion criteria at the time of the study.

Sampling technique: This took place in the cardiology clinic and echocardiography lab either in at Fedail Hospital and Alshaab Teaching Hospital. Using the comprehensive coverage of all patients who fulfill the inclusion criteria in consecutive way.

Research Tools and Methods:

We collected the data from all patients with non-ischemic dilated cardiomyopathy in their follow up visits, targeting patients who had been evaluated previously either in the clinics or being admitted and having baseline clinical assessment notes and echocardiography (named as ECHO A), the interval between each echocardiography assessment during follow up visits (patients may have more follow up visits with or without echocardiography in between) at least was 6 months duration.

Every patient should have initial assessment clinically (focused history and examination looking for evidence of failure) and echocardiography profile documented in the hospital medical notes & ECHO lab computer system. ECHO reports kept by patient were also accepted.

Data was collected using a comprehensive questionnaire. The questionnaire composed of two parts one for the baseline parameters and the second part for follow up parameters after 6 months. It was filled by the researcher after obtaining informed consent from patients and acceptance from the hospital directors and physicians caring for the patients.

For purposes of this research, baseline data was termed as data A (clinical characteristics + echo a + drug profile at baseline), while follow up data was termed as data B (NYHA class +echo b +changes in the drug profile at end of 6 months).

DATA A (retrospective): was collected in the follow up visit by:

1- Obtaining focused history for: presenting symptoms, possible causes of DCM, drug profile & their adherence to treatment
2- Referring to the patients' medical files, discharge cards, ECHO report & also by referring to ECHO lab computer system.

DATA B (prospective): all parameters were recorded at the same follow up visit in case that ECHO was done at the same day or by referring to ECHO lab computer system if it was done later.

Patients who achieved an increase of ≥ 10LV ejection fraction (LVEF) units and LV reverse remodeling (LVRR) were compared to patients who did not improve to this level.

Established IHD was ruled out as a primary cause of cardiomyopathy: by symptomatology, ECG & suggestive ECHO findings.

In this research, co-morbidities and potential causes of secondary cardiomyopathy such as HTN, DM, and history of alcohol abuse, chemotherapy exposure, arrhythmia, peripartum cardiomyopathy, or endocrinopathy all were documented.

Technique used:

Echocardiographic study: Conventional M-mode, 2-dimensional, and Doppler variables were measured in all patients according to international guidelines. Left ventricular diameters were measured at M-mode and volumes, and LVEFs were calculated at 2-dimensional echocardiography from an apical 4-chamber view using the biplane method of disks. Right ventricular areas and fractional area contraction, as well as the end systolic left atrial area, were also measured using the same approach.

- Studies (A&B) for each patient were conducted by the same operator.
- We defined reverse remodeling of the left ventricle as an increase in LVEF by at least 10% units.
- Patients who achieved an increase of ≥ 10LV ejection fraction (LVEF) units and LV reverse remodeling (LVRR) were compared to patients who did not improve to this level.

Study variables:

- Demographic data: gender, age, state of origin & address: Khartoum or other state.

- Clinical characteristic data: on heart failure at first visit / duration of HF since years / presence of AF, DM, HTN, smoking, family hx of DCM, CKD (or ESRD) or other co-morbidity

- DATA A: NYHA class at baseline + baseline ECHO + drug profile at baseline.

- DATA B: NYHA class at 6 months + follow up ECHO + drug profile at end of 6 months follow-up.

- ECHO parameters: units in mm:

- LVEDD: left ventricular end diastolic diameter
- LVESD: left ventricular end systolic diameter
- LVEF: left ventricular ejection fraction
- RVID (basal): RV Basal Diameter
- LA Diameter: Left atrial Diameter
- RA Diameter: right atrial Diameter
- Mitral regurgitation presence
- PASP: pulmonary arterial systolic pressure.
- Presence of intra-cardiac thrombus.

Data analysis: The data for numerical values will be expressed in form (mean+/- Standard division SD). Chi–square test will used to test for significant difference between the variables. A P. value < 0.05 was considered statistically significant. The results are presented in tables and graphs.

Ethical consideration:

• Ethical approval was obtained from Sudan Medical Specialization Board (SMSB), counsel of internal medicine

• Written permission was obtained from the administrative authority of the study area (Hospital).

• Study data/information used for the research purposes only. The privacy issues were be intentionally considered.

• The participation is voluntary. Any participants have own right to withdraw at any stage of the study.

Results:

This study enrolled 69 non-ischemic DCM patients; demographic characteristics of all patients are shown in Table 1 below. 25 (36%) of the study participants originally came from the northern region of Sudan (River Nile and Northern states), while 18 (26.1%) originally were from the central region (Khartoum state & its neighboring areas) which was the same percentage of patients who came from the western region. 8 patients came from southern & eastern regions (4 from each one).

Table 1: Demographic distribution of the participants (n = 69)

Demographical characteristics		Frequency	%
Gender	Male	38	55.1
	Female	31	44.9
Age in years	< 40	5	7.2
	40 – 60	38	55.1
	> 60	26	37.7
State	Northern	25	36.2
	Western	18	26.1
	Central	18	26.1
	Southern	4	5.8
	Eastern	4	5.8
Address	Khartoum	55	79.7
	Other	14	20.3

Among 69 participants, 38 (55.1%) were males & 31 (44.9%) were females (Figure 1).

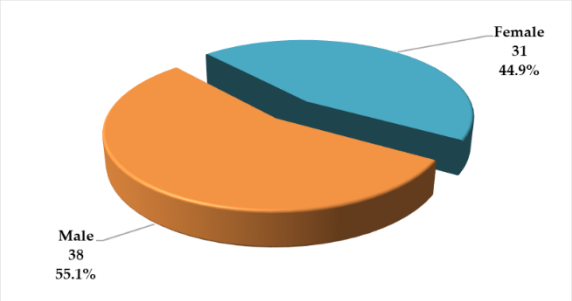

Figure 1: distribution of participants according to their gender (n = 69)

Age categories for participants were classified to 3 groups as less than 41 years, 40-60 years, & 61+ years. The frequency of first group was 5 (7.2%) patients, 38 (55.1%) patients were between 40-60 years of age & 26 (37,7%) patients were more than 60 years of age (figure 2).

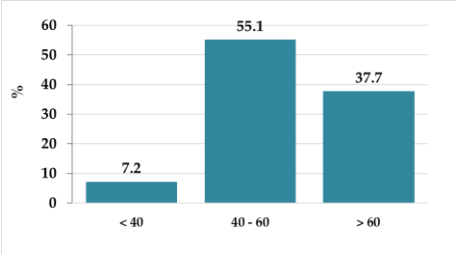

Figure 2: Age distribution of participants (n = 69)

Most (79.7%) of our patients resided in Khartoum state and the remainder were from other states (figure 3).

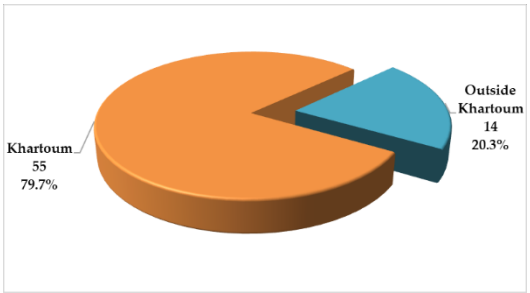

Figure 3: Geographical distribution participants (n = 69)

Baseline clinical characteristics:

50 (72.5%) of the participants were in heart failure at their first visit to the hospital at the enrollment time, while the remainder 19 (27.5%) were clinically not on heart failure which explained the response to treatment offered to them in the primary health care centers before referral. Regarding co-morbidities, 19 (27.5%) patients were diabetics & 38 (55.1%) were hypertensive. Smoking history was positive in 15 (21.7%) participants, 9 (13%) of our patients suffer from CKD or ESRD. Positive family history of DCM was seen in 5 (7.2%) of participants.

History of alcohol abuse appeared in 13 (18.8%) patients among the study participants. Peripartum cardiomyopathy patients & patients with history of malignancy who received chemotherapy they were 3 for each (Table 2).

Table 2: Distribution of participants according to their clinical characteristics (n = 69)

Clinical characteristics		Frequency	%
Clinical characteristics	On heart failure – first visit	50	72.5
	Atrial fibrillation (ECG)	10	14.5
	Diabetes mellitus	19	27.5
	Hypertension	38	55.1
	Smoking	15	21.7

	Family history of DCM	5	7.2
	CKD or (ESRD)	9	13.0
	History of alcohol use	13	18.8
	Peripartum cardiomyopathy	3	4.3
	Hx of malignancy or chemotherapy	3	4.3
	Ventricular tachycardia	1	1.4
CKD			
Stage of CKD (n = 9)	Stage 1	1	11.1
	Stage 2	3	33.3
	Stage 3	3	33.3
	ESRD	2	22.2

Table 3 below reveals the other co-morbidities among the study participants.

Table 3: distribution of participants according to their co-morbidities (n = 69)

Other co morbidities	Frequency	%
Benin prostatic hypertrophy	3	4.3
PUD	2	2.9
Thyrotoxicosis	2	2.9
Lung disease	2	2.9
Autoimmune disease	2	2.9
Chronic liver disease	1	1.4
Ischemic stroke	1	1.4
None	36	52.2
Total	69	100.0

In most of our patients, the duration of heart failure was 2 years or less, 11(15.9%) of them were newly diagnosed (Table 4 & Figure 4).

Table 4: distribution of participants according to other clinical characteristics (n = 69)

Clinical characteristics		Frequency	%
Duration since diagnosis	New	11	15.9
	≤ 1	21	30.4
	2	20	29.0
	3	16	23.2
	4	1	1.4
	5 or more	0	0.0
NYHA class at presentation	Class 1	23	33.3
	Class 2	35	50.7
	Class 3	9	13.0
	Class 4	2	2.9

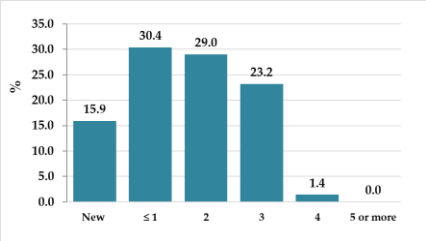

Figure 4: Distribution of participants according to duration since diagnosis (n = 69)

Most of our participants belonged to NYHA functional classes 1 to 2 at the baseline 58 (84%) patients (Table 4, Figure 5).

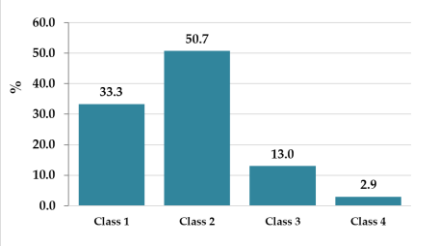

Figure 5: distribution of participants according to the **NYHA class at presentation** (n = 69)

The echocardiographic evaluation at baseline was consistent with a severe reduction of systolic function (mean LVEF 23.7%) and with a moderate left ventricular dilation (LV end-diastolic diameter: mean 58.7 mm), table 5 illustrates other parameters of echocardiography at the baseline.

Table 5: results of baseline/after six months echocardiography (n = 69)

Stage	Baseline echocardiography	O	M	Std. deviation	Min.	Max.
Base line	LV end diastolic diameter (mm)	69	58.7	4.5	45	67
	LV end systolic diameter (mm)	69	48.0	6.6	35	65
	LV ejection fraction (%)	69	23.7	5.1	15	35
	RV internal diameter (mm)	69	43.9	4.2	32	60
	LA diameter (mm)	69	43.3	3.7	32	52
	RA diameter (mm)	69	40.5	7.5	32	95
	RV systolic pressure (mmHg)	69	35.8	5.8	27	54
After six months	LV end diastolic diameter (mm)	69	53.7	7.5	30	66
	LV end systolic diameter (mm)	69	44.7	7.2	32	68
	LV ejection fraction (%)	69	30.4	6.0	20	45
	RV internal diameter (mm)	69	40.8	3.3	32	49
	LA diameter (mm)	69	39.7	3.8	30	47
	RA diameter (mm)	69	37.2	3.4	31	50
	RV systolic pressure (mmHg)	69	34.5	5.2	26	50

O = Observation, M= Mean, Min. = Minimum, Max. Maximum

Table 6 reveals that LVEF during 6 months improved slightly to reach a mean of LVEDD = 53.7 mm; whereas LVEF gradually also improved up to a mean of 30.4%.

Table 6: Echocardiography parameters initially and after 6 months follow-up as a mean value (n = 69)

Echocardiography parameters	Baseline (Mean)	6 months (Mean)	Diff.	P value
LV end diastolic diameter (mm)	58.7	53.7	-5	< 0.001
LV end systolic diameter (mm)	48.0	44.7	-3.3	< 0.001
LV ejection fraction (%)	23.7	30.4	+6.7	0.003
RV internal diameter (mm)	43.9	40.8	-3.1	< 0.001
LA diameter (mm)	43.3	39.7	-3.6	< 0.001
RA diameter (mm)	40.5	37.2	-3.3	0.005

RV systolic pressure (mmHg)	35.8	34.5	-1.3	0.003

For all patients, NYHA functional class had significantly improved, all the patients were in the first 2 classes (NYHA 1 & 2) by the end of this study (p value < .001) (Table 7).

Table 7: **NYHA class**ifications initially and after six months follow-up (n = 69)

NYHA class	Baseline		After six months	
	Freq.	%	Freq.	%
1	23	33.3	58	84.1
2	35	50.7	11	15.9
3	9	13.0	0	0.0
4	2	2.9	0	0.0
Total	69	100.0	69	100.0

P-value < 0.001

Intra-cardiac thrombus had complicated 8 (11.6%) of our participants at the baseline & the percentage remain the same at the end of 6 months duration (Table 8).

Table 8: Presence of LV thrombus initially and after six months follow up (n = 69)

LV thrombus	**Baseline**		**After six months**	
	Freq.	**%**	**Freq.**	**%**
Yes	8	11.6	8	11.6
No	61	88.4	61	88.4
Total	69	100.0	69	100.0

P value = 1.0

Regarding detection of mitral regurgitation, initially at the baseline were 24 (34.7%) of our patients were discovered to have moderate to severe MR, and by the end of the follow up duration significant improvement had occurred, and the total number of patients who were discovered to have MR was 21 (30.4%) with mild to moderate MR & all patients with severe MR had a remarkable regression in their regurgitation degree (p value = 0,0017) (Table 9).

Table 9: Mitral regurgitation initially and after six months follow up (n = 69)

MR	Baseline		After 6 months	
	Freq.	%	Freq.	%
Severe	9	13.0	0	0.0

Moderate	15	21.7	15	21.7
Mild	0	0.0	6	8.7
None	45	65.2	48	69.6
Total	69	100.0	69	100.0

P-value = 0.0017

Reverse remodeling outcome:

Among our participants, LVRR was noted in 17 (24.6%) patients according to definition, while 52 (75.4%) of patients didn't develop LVRR.

Regarding non-LVRR group, 14 (20.3%) patients had considerable improvement in their LVEF% but not fulfilling the definition of reversed remodeling, LVEF% improvement was between 7 and 9%. 38 (55.1%) of our participants showed mild or non-improvement in their LVEF% (Table 10, Figure 6).

Table 10: distribution of participants according to the frequency of RR (n = 69)

Reverse remodeling	B (M)	6 (M)
Reverse remodeling (increased LVEF with 10 % or more)	17	24.6
Improved (increased LVEF with 9 – 7 %)	14	20.3
None (increased LVEF with less than 7%)	38	55.1
Total	69	100.0

B = Baseline, M = Mean, 6 = After 6 months

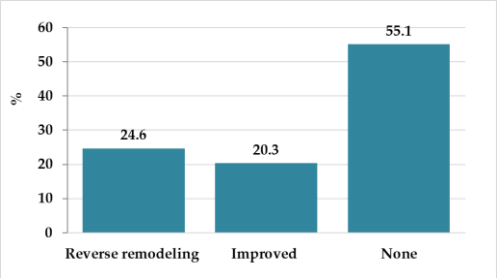

Figure 6: Distribution of participants according to the frequency of RR (n = 69)

Demography & RR:

LVRR frequency among study participants appeared to be related to their age, 13 (76.5%) of 17 patients who have LVRR were 40-60 years old, while 3 (17.6%) were under 40 years old, one patient of the 61+ group demonstrated LVRR (P value 0,004) (Table 11).

Table 11: association between general demographical characteristics with the presence of RR (n = 69)

Patients' characteristics		Reverse remodeling						P value
		Yes (n = 17)		No (n = 52)		Total (n = 69)		
		Freq.	%	Freq.	%	Freq.	%	
Age – years	< 40	3	17.6	2	3.8	5	7.2	0.004
	40 – 60	13	76.5	25	48.1	38	55.1	
	> 60	1	5.9	25	48.1	26	37.7	
Gender	Male	7	41.2	31	59.6	38	55.1	0.1850
	Female	10	58.8	21	40.4	31	44.9	
Address	Khartoum	12	70.6	43	82.7	55	79.7	0.213
	Other	5	29.4	9	17.3	14	20.3	

Heart failure duration & RR:

14 (82.3%) patients of LVRR group their heart failure duration was less than 2 years meanwhile 34 (65,4%) patients non-RR group most of them were diagnosed more than 2 years (Table 12).

Table 12: relation between LVRR & Heart failure duration (n = 17)

Heart failure duration before enrollment		LVRR group (n=17)		Non-LVRR group (n=52)		P-value
		Frequency	%	Frequency	%	
Duration since diagnosis (years)	New or ≤ 1	5	29.4	6	11.5	< 0.001
	2	9	53	12	23.1	
	3	3	17.6	18	34.6	
	4	0	0.0	16	30.8	
	5 or more	0	0.0	0	0.0	

Baseline clinical characteristics & LVRR:

Among different co-morbidities, only 2 showed a significant relation to LVRR. Sinus rhythm was apparent in all patients who developed reverse remodeling (p-value 0.048) and the second factor was the absence of smoking history, which was observable in 16 (94.1%) patients among LVRR group. other co-morbidities detailed in Table 13.

Table 13: Clinical characteristics vs presence of RR (n = 69)

Other clinical characteristics		Reverse remodeling						P-value
		Yes (n = 17)		No (n = 52)		Total (n = 69)		
		Freq.	%	Freq.	%	Freq.	%	
On HF – 1st visit	Y	12	70.6	38	73.1	50	72.5	0.842
	N	5	29.4	14	26.9	19	27.5	
Atrial fibrillation (ECG)	Y	0	0.0	10	19.2	10	14.5	0.048
	N	17	100.0	42	80.8	59	85.5	
DM	Y	6	35.3	13	25.0	19	27.5	0.522
	N	11	64.7	39	75.0	50	72.5	
HTN	Y	7	41.2	31	59.6	38	55.1	0.185
	N	10	58.8	21	40.4	31	44.9	
Smoking	Y	1	5.9	14	26.9	15	21.7	0.046
	N	16	94.1	38	73.1	54	78.3	
Family hx of DCM	Y	1	5.9	4	7.7	5	7.2	0.698
	N	16	94.1	48	92.3	64	92.8	
CKD or ESRD	Y	2	11.8	7	13.5	9	13.0	0.750
	N	15	88.2	45	86.5	60	87.0	
History of alcohol use	Y	1	5.9	12	23.1	13	18.8	0.24
	N	16	94.1	40	76.9	56	81.2	
Peripartum cardiomyopathy	Y	1	5.9	2	3.8	3	4.3	0.12
	N	16	94.1	50	96.2	66	95.7	
History of malignancy or chemotherapy	Y	0	0	3	4.3	3	4.3	0.33
	N	17	100	49	95.7	66	95.7	

Ventricular tachycardia	Y	1	5.9	1	1.9	2	1.4	0.15
	N	16	94.1	51	98.1	67	98.6	

Pregnancy associated cases were 3, one of them developed RR.

LVEDD in RR group:

LVEDD measurements were significantly improved (decreased) among RR group from mean of 59 mm to 47 mm after 6 months (p value = < 0.001), non-RR group had observable decrease in their LVEDD from 58 mm to 55 mm (Table 14).

Table 14: LVEDD measurements mean in RR & Non-RR group at both follow up visits:

MEAN LVEDD in mm	Initial	After 6 months	P-value
RR group (n = 17)	59.05	47.82	< 0.001
Non-RR group (n = 52)	58.53	55.59	< 0.001
Total (n = 69)	58.67	53.68	0.004

Implications of RR:

During follow-up, 5 (29.4%) readmissions observed for decompensated HF due to different exacerbating factors while the remaining 12 (70.6%) were not re-admitted during study period. In comparison with non-LVRR group, readmission percentages were higher, reaching 38.5% (20) readmissions due to different causes (Table 15).

Table 15: association between admission with HF and the presence of RR (n = 69)

	Reverse remodeling						**P-value**
	Y (n = 17)		**N (n = 52)**		**Total (n = 69)**		
	Freq.	**%**	**Freq.**	**%**	**Freq.**	**%**	

Admission with HF	**Y**	5	29.4	20	38.5	25	36.2	0.500
	N	12	70.6	32	61.5	44	63.8	
Total		17	100.0	52	100.0	69	100.0	

Regarding NYHA functional class all the candidates they were having class 1or 2 by the end of the follow up, all patients, except one, with RR had NYHA class one (Table 16).

Table 16: NYHA functional class across and reversibility RR & non-RR group:

NYHA class	NYHA I	NYHA II	Total
Non- RR group	42 (80.7 %)	10 (19.3 %)	52 (100%)
RR group	16 (94.1 %)	1 (5.9 %)	17 (100%)

Regarding the implications of RR In our patients with non-ischemic DCM, there was neither detectable significant (severe) mitral regurgitation nor intra-cardiac thrombus at the end of 6 months duration (Tables 17 and 18).

Table 17: Intra-cardiac thrombus and it's relation to RR group:

Intra-cardiac Thrombus	**Present**	**Absent**	**Total**
Non- RR group	**8 (15.4%)**	**44(84.6%)**	**52(100%)**
RR group	**0(0%)**	**17 (100%)**	**17(100%)**
Total	**8 (11.6 %)**	**61 (88,4%)**	**69 (100%)**

Table 18: Mitral regurgitation and it's relation to RR group:

MR	Mild	Moderate	Severe	None	Total

Non-RR group	4(7.7%)	10(19.23%)	17(32.7%)	37(71.1%)	52(100%)
RR group	2 (11.7%)	5 (29.4 %)	0 (0%)	10 (58.8%)	17(100%)

Treatment and RR:

Neurohormonal drug treatment with ACE inhibitors and beta-blockers was tailored in the majority of patients (94% for both in RR group, 76% & 96% for non-RR group) toward the target doses. Spironolactone also was also tailored in RR group to near 88% (Tables 19 and 20).

Table 19: drugs used according to presence of RR in the baseline and after six months outcome (n = 69)

Drug group	Drug	Dose (mg)	Baseline				After six months			
			RR (n = 17)		No RR (n = 52)		RR (n = 17)		No RR (n = 52)	
			F.	%	F.	%	F.	%	F.	%
ACEI	Lisinopril	5 or less	4	23.5	6	11.5	0	0.0	1	1.9
		10+	1	5.9	2	3.8	5	29.4	7	13.5
	Ramipril	5 or less	0	0.0	2	3.8	1	5.9	1	1.9
		7.5	1	5.9	0	0.0	0	0.0	0	0.0
		10+	0	0.0	0	0.0	1	5.9	0	0.0
ARBs	Candesartan	4	1	5.9	1	1.9	0	0.0	0	0.0
		8	7	41.2	20	38.5	1	5.9	2	3.8
		16	1	5.9	5	9.6	8	47.1	23	44.2
		32	0	0.0	0	0.0	0	0.0	1	1.9
	Valsartan	80	0	0.0	2	3.8	0	0.0	1	1.9
		160	0	0.0	4	7.7	0	0.0	4	7.7

	Losartan	**50**	0	0.0	5	9.6	0	0.0	0	0.0
		100	1	5.9	3	5.8	0	0.0	0	0.0
β-blockers	**Bisoprolol**	**2.5**	6	35.3	22	42.3	0	0.0	3	5.8
		5	9	52.9	28	53.8	14	82.4	42	80.8
		7.5	1	5.9	1	1.9	1	5.9	3	5.8
		10	0	0.0	0	0.0	1	5.9	2	3.8
	Propranolol	**80**	1	5.9	1	1.9	0	0.0	0	0.0
Diuretics	**Furosemide**	**40**	5	29.4	21	40.4	12	70.6	39	75.0
		80	11	64.7	29	55.8	3	17.6	8	15.4
		120 +	0	0.0	1	1.9	0	0.0	0	0.0
	Hydrochlorothiazide	**12.5**	0	0.0	4	7.7	0	0.0	2	3.8
		25 +	0	0.0	0	0.0	0	0.0	2	3.8
Spironolactone		**6.25**	2	11.8	2	3.8	1	5.8	1	1.92
		12.5	4	23.5	15	28.8	0	0.0	13	25
		25	3	17.6	7	13.5	10	58.8	19	63.5

F = Frequency

Table 20: drug groups used according to the presence of RR in the baseline and after six months outcome (n = 69)

Drug group		Baseline				After six months			
		RR (n = 17)		No RR (n = 52)		RR (n = 17)		No RR (n = 52)	
		F.	%	F.	%	F	%	Freq.	%
ACEI and ARBS		16	88.3	50	96	16	94.2	40	76.8
B-blockers		17	100	52	99.9	16	94.2	50	96.2
Diuretics/ frusemide		17	94.1	52	99.9	15	88.2	51	98
Spironolactone		16	83.3	50	96	15	88.2	13	25

Discussion:

Non-ischemic DCM contains various etiologies with various time course for RR response, so we expected that most of our RR group was developed DCM due to acute myocardial injury (e.g. myocarditis) rather than idiopathic pathology which is exhibit RR in more time in comparison to acute etiologies. That is suggested by findings by Givertz and colleagues who documented rates of LVEF improvement (to LVEF >50%) of 60% to 100% (30). In a tertiary care center cohort of over 1,800 patients with HF, only 10% of patients had HFiEF (23).

Our study was aiming to detect RR within 6 months duration which is seems reasonable because that implies need for assessment of device therapy, keeping in mind that heart failure guidelines recommend postponing the decision on primary prevention implantable cardioverter defibrillators for DCM by at least 3 months, allowing the process of RR to take place (70).

Merlo and colleagues concluded that the best timing of evaluation remains debated. After removing any possible cause of LV dysfunction, if detectable at diagnosis, it is reasonable to evaluate patients 3 to 9 months after implementation of optimal medical treatment in order to identify candidates for ICD implant (64).

Arad and colleagues reported timings for first detection of LVRR in their study as follows:12 % of patients with delayed LVRR, categorized as patients without LVRR similar to those inclined towards poor prognosis in previous studies, had better prognosis equivalent to those with early LVRR (65). While improvement in LVEF may be the simplest and most effective way to risk-stratify the DCM population, decreasing the LV diastolic dimension is the most relevant physiological indicator of beneficial remodeling (42).

Wilcox and colleagues found that ejection fraction increased over 10% in 28.6% of patients (44). Merlo and colleagues found that LVRR was recognized in 37% of patients analyzed (14).

Duberstein et al. stated that reverse remodeling is a common finding in DCM under contemporary therapy involving ~25% of patients with established disease (67).

Fewer percentages were found for RR detection as in Val-HeFT (Valsartan Heart Failure Trial) which found, only 9% of patients selected for analysis experienced LVEF improvement to 40% during the first 12 months of follow-up (66).

Our study was not aiming to study & compare the pharmacological therapies as all patients were treated according to the guidelines. About 80–86% were treated with a β-blocker, 84–90% with an ACE inhibitor or ARB. Yet, we found that a higher β-blocker dose predicted improvement of LVEF, these findings are in agreement with the literature and reinforce the recommendation to seek the maximal tolerated dose of β-blockers (71)**.**

Punnoose and colleagues found that HFiEF patients were younger and less likely to have coronary disease compared with those with HFrEF, whereas rates of atrial fibrillation, hypertension, and diabetes were similar (30).

14 (82.3%) patients of LVRR group their heart failure duration was less than 2 years, meanwhile non-RR group most of them were diagnosed more than 2 years, 34 (65.4%) patients. Arad and colleagues conclude that shorter disease duration was an independent predictor of improvement (42)

Ikeda and colleagues found that among the clinical parameters during the first 6 months, reduced LVEDD could be a significant factor in distinguishing between the delayed and no LVRR groups (65).

Our study found that pregnancy associated cases were 3, just one of them achieved. RR A study found that peripartum cardiomyopathy or in association with pregnancy is associated with better prognosis (42).

Kuperstein and colleagues found that reduction in the severity of functional MR is quite prevalent in patients with DCM who present with significant MR and reverse remodel during follow-up (67).

Limitations:

An important limitation of this study is that the study period was accompanied by a major political turmoil in Sudan (December 2018 revolution) which affected the stability of patients' movement and their attendance to their appointments timetable especially improving. HF patients who are under the focus of this study & this in turn had a major influence on our sample size.

A lot of patients were excluded from the study due to deficient data on their medical notes (e.g. Full echocardiography parameters) or lack of accurate documentation in Alshaab Teaching Hospital.

Our study did not assess the frequency of death, referral for device therapy or even cardiac transplantation in many DCM patients.

Application of HF guidelines regarding optimization of therapy is variable among junior staff working in cardiology referral clinics which led to exclusion of many patients.

A considerable number of patients who felt symptoms relief they didn't attach to their follow-up schedule in cardiology referral clinics.

Also using echocardiography as a tool for follow up is not fully practiced in stable DCM patients in cardiology clinics, many doctors they depend on vital signs, clinical examination & U&E in their follow up, & just rely referring for ECHO assessment for cases that deteriorates.

Conclusion:

The present study concludes that, cardiac reversed remodeling is important treatment goal & it can be achieved in the first 6 months of follow up with fully optimized medical therapy. Our study found that 17 (24.6%) patients they developed RR, while 14 (20.3%) had

considerable improvement in their LVEF % but not fulfilling the definition of err and 38 (55.1%) showed mild or non-improvement in their LVEF %.

Recommendations:

It is Important to raise the awareness among DCM patients regarding the possible improvement in their LVEF and to share & discuss the results of echocardiography that may encourage them to be maximally adhere to their medications, punctual attendance to their appointments of follow-up.

We must consolidate the importance of optimization of heart failure medications among DCM patients for the junior staff working in cardiology clinics.

We must stress on importance of using echocardiography as a tool for follow up for DCM patients at least at 3,6,9 months intervals.

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