Cardiac Rehabilitation for Secondary Prevention of Cardiovascular Diseases

By

S. Hammad Jafri

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Project Mentor: Hicham H Skali, M.D., M.Sc. FACC

I have reviewed these projects. It represents work done by the author under my guidance.

Thesis Committee Members:

Candidate: S. Hammad Jafri, M.D.

Primary Mentor: Hicham H Skali, M.D., M.Sc. FACC

External Content advisor: Amil Shah, M.D.

MMSCI Program Representative: Michael Mendelson, M.D., Sc.M.

Independent External Expert: Akshay Suvas Desai, MD, MPH

Program's Directors: Ajay Singh, M.B.B.S, M.B.A., F.R.C.P., and

Finnian McCausland M.B.B.Ch., M.M.Sc., F.R.C.P.I., P.G. CertMedEd

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Overview of thesis papers (Background and context)

Outpatient cardiac rehabilitation programs provide supervised exercise training in conjunction with other secondary prevention interventions. They are designed to speed recovery from acute cardiovascular events such as myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, angina, heart failure, heart transplant and after heart valve procedure to improve quality of life[1].

Aortic Stenosis is one of the most common types of valvular heart disease in elderly with reported prevalence as high as 12-26%[2]. The most common etiology of mitral stenosis is rheumatic heart disease; however, it is not common that the disease remains undiagnosed up until an advanced age. Functional mitral stenosis related to massive annular calcification and reduced leaflet excursion has been reported in 2.5-18.0% of elderly patients. Mitral regurgitation is the most frequent valvular heart disease in patients over the age of 65 years. Elderly patients account for about 40% of all patients with mitral regurgitation and 4.5% are over 80 years of age. Mitral valve diseases are increasing in prevalence and require valve replacement in severe diseases. Patients after mitral valve procedure do go to cardiac rehabilitation but minimal clinical studies have done to show magnitude of benefit for cardiac rehabilitation in this patient population. Randomized clinical trials have shown improvements (both physical and psychological) in patients undergoing cardiac rehabilitation after aortic valve replacement, so we compared mitral valve patients with them to see any benefits[1-4]. We evaluated baseline exercise capacity and psychological well-being for mitral valve patients participating in cardiac rehabilitation and compare physical and psychological outcomes between mitral valve and aortic valve patients.

In our 2nd paper we discussed importance of guideline directed medial therapy in cardiovascular diseases. As cardiac diseases are the most common cause of morbidity and mortality in USA, it is important to diagnose and treat effectively for secondary prevention of cardiovascular diseases. Patients with coronary artery disease & congestive heart failure need to be on guided medical therapy for recovery from primary event as well as for prevention of further cardiovascular events. Cardiac Rehabilitation programs have shown improvements in secondary prevention of cardiovascular events; however, no clinical studies are available to show prevalence of guideline directed medical therapy in this patient population[4-6]. Also, we can identify predictors of better medication prevalence in patient with coronary artery disease and heart failure.

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Physical and Psychological Wellbeing Effects of Cardiac Rehab on Patients Following Mitral Valve and Aortic Valve Procedures

S. Hammad Jafri, MD[1,2]; Pavel Huschsa, MBBS[2]; Pranav Dorbala, BS[2]; Gisele Bousquet, MS, RN[3]; Christine Lutfy, RN[3]; Jodi Klein, PT[3]; Lindsay Sonis, RN[3]; Donna Polk, MD, MPH[2,3]; Hicham Skali, MD, MSc[2,3]

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1. Master of Medical Sciences in Clinical Investigation Program, Harvard Medical School, Boston, MA
2. Cardiovascular division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA
3. Cardiac Rehabilitation program, Brigham and Women's Hospital, Foxborough, MA

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*Corresponding Author
Hicham Skali, MD, MSc, FACC
Cardiovascular Division, Department of Medicine
Brigham and Women's Hospital
75 Francis Street
Boston, MA, 02115
Phone: 857-307-1988
Email: hskali@bwh.harvard.edu

ABSTRACT

Introduction

Patients participating in cardiac rehabilitation following an aortic valve procedure demonstrate improvements in physical capacity and psychological well-being. The primary aims of this study were to evaluate baseline exercise capacity and psychological well-being for mitral valve patients participating in cardiac rehabilitation and to compare physical and psychological outcomes between mitral valve and aortic valve patients.

Purpose

To compare change in 6-minute walk distance, anxiety , depression and overall quality of life scores between subjects who had surgical mitral valve procedure and those who had surgical aortic valve procedure. We hypothesized that cardiac rehabilitation will equally improve physical capacity and well-being in participants following mitral valve procedure when compared to aortic valve procedure.

Design

Retrospective cohort analyzing characteristics of patients after aortic valve procedure and mitral valve procedure who underwent cardiac rehabilitation.

Methods

Primary endpoint was improvement in 6-minute walk distance. Secondary endpoints included change in exercise minutes per week, depression scores (PHQ-9) , anxiety scores (GAD-7) and overall quality of life (COOP) scores.

Results

Between January 2015 and December 2019, 94 patients who underwent an aortic valve procedure and 46 patients who underwent mitral valve were enrolled prospectively in cardiac rehabilitation. Patients who had double valve procedure & TAVR were excluded from this analysis. There were no baseline differences between age or gender between groups. Patients in the mitral valve procedure group had lower prevalence of diabetes, hypertension and coronary artery disease and were less likely to be on statins. Mitral valve patients had same exercise capacity at baseline (mitral valve: 7 METs (±3) vs. aortic valve: 7 METS (±3), p=0.46). Overall rates of cardiac rehabilitation completion were similar in both groups (81% in mitral valve group vs. 71% in aortic valve group, p=0.22). At the completion of their cardiac rehabilitation program, patients with mitral valve procedures and those with aortic valve procedures had similar improvements in their six-minute walk distance (mitral valve: 173 feet (125, 238 feet) vs. aortic valve 197 feet (121, 295), p=0.42); Exercise minutes per week (mitral valve: 90 minutes (45, 175) vs aortic valve: 80 minutes (40, 130), p=0.44). Changes in anxiety (GAD-7), depression (PHQ-9) and COOP scores were minimal but similar between the two groups.

Conclusions

Cardiac rehabilitation participation results in similar improvements in physical activity between patients with mitral valve procedures and those with aortic valve procedures. Psychological well-being and quality of life scores improved minimally and similarly between the two groups. Larger studies are needed to confirm these findings; in the meantime, patients with mitral valve procedure should continue to be encouraged to participate in cardiac rehabilitation.

Introduction

Cardiac Rehabilitation (CR) is a multifaceted comprehensive secondary prevention program that has been shown to improve quality of life and cardiovascular (CV) survival in eligible patients following a cardiac event including valvular heart procedures[1]. The prevalence of valvular heart disease in increasing rapidly among the elderly population in United States with more patients undergoing valvular replacements[2]. It is estimated that approximately 13% of people developed either aortic or mitral valve disease by 75 years of age and meet the clinical indications of a procedure over subsequent 5 years[3]. In addition to quality valve replacement, the post-operative recovery period is critical to allow patients to achieve improved quality of life and cardiac rehabilitation can help these patients recover for a faster return to normal life.

CR is beneficial for patients following an Aortic Valve (AV) procedure[4-7] as participation in CR demonstrates improvements in physical capacity, psychological well-being and overall mortality in valvular heart disease patients[7-9], there is however little data about the magnitude of the effect of CR on patients following mitral valve (MV) procedures. Also, patients after MV surgery[10-13] have demonstrated improved exercise capacity but it is unknown if CR can further improve it or not. We aimed to compare the extent of physical and psychological changes following participation in CR between patients who underwent an AV or MV procedure. We hypothesized that patients after MV repair benefit similarly as AV patients from the exercise training component of CR.

Methods

Comprehensive data was collected from consecutive patients enrolled in the Brigham and Women's Hospital CR program in Foxborough, MA. For this analysis, patients who were referred for a diagnosis of Surgical Aortic Valve Procedure (SAVP) or Surgical Mitral Valve Procedure (SMVP) were included. Patients who were referred for non-valvular indications, and those following double valve procedures (aortic and mitral) were excluded. Patients referred following percutaneous valvular procedures were included in a separate sensibility analyses.

The primary outcome was the change in 6-minute walking distance (6MWD) between beginning and end of CR. Secondary outcomes included changes in: Exercise Minutes per Week (EMW), overall health scores determined by The Dartmouth Cooperative Functional Assessment (COOP), depression scores by Patient Health Questionnaire-9 (PHQ-9) and anxiety scores by General Anxiety Disorder-7 (GAD-7). Exercise capacity was assessed by exercise tolerance test and/or 6MWD. Total exercise minutes per week (EMW) was collected from patient's questionnaire. All parameters were collected at the beginning and end of the CR program, except the exercise tolerance test which was only performed only at the beginning of CR. The study protocol was approved by the Internal Review Board at Brigham and Women's Hospital

Hypertension (HTN), coronary artery disease (CAD), diabetes (DM) and hyperlipidemia (HLD) were recorded at the time of entry to CR and smoking history was self-reported. Prescribed medications were reviewed and confirmed with the patient at entry to CR. Details about procedures like Transcatheter Aortic Valve Replacement (TAVR), surgical aortic valve repair or replacement and mitral valve repair or replacements were gathered retrospectively via chart review.

The exercise training program is similar to that performed at most rehabilitation programs around the United States. Generally, individuals exercised for 45 to 60 minutes per CR session on a variety of modalities including: treadmills, elliptical trainers, rowing machines, cycle and arm ergometers. Upper body strength training began 3-months post-operatively. In addition, there were weekly sessions of 60 minutes which included counselling and education on secondary prevention topics including nutrition and stress reduction.

Statistical Analysis

Data cleaning was done and patients with missing values at enrollment were not included. For the main analysis, subjects were grouped into SAVP and SMVP. In a sensitivity analysis, SMVP patients were compared to the overall aortic valve group including both surgical and percutaneous patients (SAVP and TAVR). Subsequently, SAVP subjects were compared to TAVR patients.

Values are presented as mean ± standard deviation, median with interquartile range, frequencies or percentage. T-test and Wilcoxon signed rank test was used to compare continuous variables between groups. A proportion of patients did not complete the CR program and did not undergo a final 6MWD test. While the distribution of 6MWD Pre-CR was not normally distributed, the change in 6MWD was normally distributed. We did a retrospective power size calculation to detect statistical difference among the two groups, to detect a significant difference of 120 feet among SAVP and SMVP for primary outcome, we needed 11 patients in each group (with 80% power and 5% alpha). Regression analysis was used to determine which variables independently correlated with change in 6MWD. Multivariable adjustment model included: age, gender, body mass index (BMI), MVP vs. AVP, 6MWD, CAD, exercise minutes per week, PHQ-9, GAD-7 and COOP scores (all at baseline). Variables included in regression analysis were selected by clinical criteria to see if they had significance or if they had statistical significance in univariate model. A level of significance of $P < 0.05$ was used for statistical significance. Statistical analyses were carried out using Stata statistical package (Stata 15.1).

Results

Between January 2015 and December 2019, 828 subjects participated in the CR program, including 140 (17%) following a surgical AV or MV procedure as described in **figure 1**. Mean age was 64 ± 12 years, with 33.5% female gender, and 46/140 (33%) patients were enrolled following an MVP. Demographic and clinical characteristics by type of valvular procedure are listed in table 1.

HTN, DM and CAD were less frequent among patients in the SMVP group. There were 111/140 (79%) subjects who underwent an exercise tolerance test (ETT) prior to CR enrollment. During the ETT, subjects in the SMVP group displayed a lower resting systolic BP (125± 15 vs. 133±18 mmHg, p=0.02) and a higher resting HR (79±12 vs. 71± 14 bpm, p<0.01) than those in the SAVP group. Use of cardiovascular medications was similar between the two groups, except for statins which were more frequently prescribed in the SAVP group (p=0.02). HbA1c values, total cholesterol and ejection fraction were similar in both groups. Rates of completion of the CR program were not statistically different (71% in SAVP group vs. 81% in SMVP group, p=0.22).

At baseline, there was no difference between the SAVP and SMVP groups in terms of aerobic capacity on exercise testing (7 ± 3 METs in SAVP group and 7 ± 3 METs in SMVP group, p=0.46), or 6MWD (SAVP 1394 [1145, 1648] vs. 1460[1295, 1595] feet in SAVP group vs. SMVP group, p=0.59). At baseline depression scores, anxiety scores and COOP scores were low but similar among both groups **(Table 1).**

Table 2 describes changes in parameters between beginning and end of CR. Overall, both groups improved their 6MWD without a statistically significant difference (median (IQR): SAVP group: 197 (121, 295) feet or 14% (increase from baseline) vs. 173 (125, 238) feet or 12% (increase from baseline) in SMVP group, p=0.42) **(figure 2).** Improvements in EMW following CR were also similar among both groups (median (IQR): SAVP group: 80 (40, 130) or 133% (increase from baseline) vs. 90 (45, 175) or 120% (increase from baseline) in SMVP group, p=0.44). Psychological health scores improved with reduction in GAD-7, PHQ-9 and COOP scores but changes in scores were not statistically different between the two groups (**Table 2**).

In a multivariable predictor model, younger age and a lower baseline 6MWD were the strongest predictors of improvement in 6MWD. The type of valvular disease or valvular procedure did not affect the change in 6MWD (Table 3).

Supplemental table 4 compares characteristics and outcomes of patients among SMVP with all aortic valve patients including SAVP and TAVR. Among subgroup comparison between TAVR group and SAVP, TAVR patients were older than in the SAVP. Patients in the TAVR group also had lower functional capacity (lower MET) and lower 6 MWD. Improvements were not statistically different between groups (supplemental Table 5).

Discussion

Our study demonstrates that in a large contemporary cohort of patients enrolled in CR following SAVP or SMVP, improvements in physical and psychological wellbeing is comparable between each valve group. While our study groups experienced similar improvements in exercise capacity following CR participation, significant differences at baseline exist between the groups. SMVP patients had similar baseline exercise capacity as SAVP patients, however the SMVP group had less comorbid conditions. Among SMVP patients, HTN, DM and CAD were less prevalent then SAVP group, however after CR, the change in 6MWD and EMW were similar to SAVP group.

SMVP patients achieved similar decreases in PHQ-9, GAD-7 and COOP scores after CR as SAVP patients. Lower scores are better in terms of depression (PHQ-9)[14], anxiety (GAD-7)[15] and overall quality of life (COOP)[16]. The majority of patients did have low baseline psychological health scores, however overall scores (PHQ-9, GAD-7 and COOP) decreased even further among both groups after CR completion indicating an improvement in psychological health.

Our prediction model shows that younger age and less 6MWD before CR is associated with better change in overall outcome. It is obvious that younger patients can achieve higher difference in 6MWD but unclear how lower 6MWD before CR can cause a better outcome. It is possible that patients who already have better exercise capacity are less motivated, however majority of our patients did individually achieve higher 6MWD after CR as mentioned in figure 2.

Within the AV subgroup, the patients undergoing SAVP were younger those undergoing TAVR. SAVP patients had a higher baseline exercise capacity (6MWD and EMW) and were able to achieve an even greater exercise capacity as measured by 6MWD and EMW than TAVR group. Changes in both 6MWD and EMW were similar and not statistically significant.

It has been previously reported that AV patients entering CR have low exercise capacity and they experience significant improvements after CR[17-18]. While previous studies have demonstrated improvements in exercise capacity for post-surgical AV patients participating in CR[19-23], less well-studied is the effect of CR following SMVP compared with patients who had undergone SAVP procedure. Our study confirms that CR is effective for patients undergoing SAVP and SMVP.

In a recently published study, risk factors such as obesity and sedentary lifestyle are predictors of poor exercise capacity after mitral valve surgery[9]. One of the benefits of CR is the focus on lifestyle modifications which can improve risk factors such as obesity and sedentary lifestyle. MV surgery has shown to be associated with improved exercise capacity[10-13] by itself, however our study shows that CR is an effective intervention, and if utilized properly can further improve exercise capacity in MV patients after surgery. New technology, such as smartphones and accelerometer-based eHealth interventions[24], can also be utilized to increase physical exercise and achieve CR goals, if traditional CR cannot be achieved.

This is a single center study and patient selection may vary between centers. The study design was observational and non-randomized. The study was a moderate size and might have unknown confounding bias as a result of being an observational study. For our regression analysis, only patients who completed CR were included as CR completion rates were not 100%.

Given that CR is the standard of care[25], randomization would not have been appropriate. Despite the lack of a control group, our results are relevant as they represent the typical cardiac rehabilitation population.

Conclusion

Patients who underwent SMVP demonstrated similar improvements in exercise capacity as those who underwent SAVP following participation in CR. Psychological well-being and quality of life scores improved minimally, and similarly, between the two groups. Larger studies are needed to confirm these findings. In the meantime, all patients undergoing valvular procedures, including those undergoing mitral valve interventions should continue to be encouraged to participate in CR.

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Table 1: Baseline Clinical and demographic characteristics (N=140)

		SAVP (N=94)	SMVP (N=46)	P Value*
Age (years)		64 ± 12	64 ± 13	0.91
Female (% of total)		28 (30%)	19 (41%)	0.18
Weight (lbs.)		204 ± 48	186 ± 50	0.04
Body Mass Index (kg/m^2)		30 ± 7	28 ± 5	0.05
Risk category • Low • Medium • High		 31 (34%) 38 (41%) 23 (25%)	 12 (27%) 15 (34%) 17 (39%)	0.26
ETT data	Baseline Heart Rate (beats/m)	71 ± 14	79 ± 12	<0.01
	Peak Heart Rate (beats/m)	120 ± 25	119 ± 24	0.94
	Baseline SBP (mmHg)	133 ± 18	125 ± 15	0.02
	Baseline DBP (mmHg)	76 ± 10	76 ± 9	0.96
	Peak exercise SBP (mmHg)	152 ± 24	146 ± 22	0.14
	Peak exercise DBP (mmHg)	74 ± 11	73 ± 10	0.42
	Exercise Test METS	7 ± 3	7 ± 3	0.46
Risk Factors • Hypertension • Diabetes Mellitus • Current smoker • Hyperlipidemia • Coronary Artery Disease • Congestive Heart failure		 81 (88%) 23 (25%) 16 (18%) 67 (73%) 30 (32%) 7 (7%)	 33 (73%) 2 (4%) 3 (7%) 27 (60%) 5 (11%) 6 (13%)	 0.03 0.01 0.08 0.13 <0.01 0.28
Glycated Hemoglobin A1C (Patients with Diabetes = 28)		5.9 ± 0.9	5.6 ± 0.7	0.13
Total Cholesterol (mg/dl)		151 ± 39	161 ± 38	0.24
Ejection Fraction		58 ± 12	56 ± 12	0.44
Medication • β Blocker • Calcium Blocker • ACEi/ARB • Statin		 76 (81%) 12 (13%) 32 (34%) 65 (69%)	 35 (76%) 5 (11%) 12 (26%) 22 (48%)	 0.51 0.75 0.34 0.02

Completed Cardiac Rehab (% of total)	65 (71%)	35 (81%)	0.22
6 MWD (ft)	1394 (1145, 1648)	1460 (1295, 1595)	0.59
EMW† (minutes)	60 (1, 120)	75 (1,130)	0.52
GAD7‡	1 (0,4)	2 (0,3)	0.88
PHQ9§	3 (1, 6)	2 (1,3)	0.14
COOP††	18 (15, 22)	18 (15, 22)	0.74

*P value comparing Aortic and Mitral group
**6 Minutes walking distance
† Exercise Minutes per week
‡ Anxiety scores
§ Depression scores
†† Overall health quality

Table 2: Clinical and demographic characteristics Pre and Post Cardiac Rehab (N=140)

	SAVP N=94	SMVP N=46	P Value*
Weight (lb)			
• Pre CR	204 ± 48	186 ± 50	
• Post CR	199 ± 44	178 ± 43	0.02
• Change	- 1 ± 7	-1 ± 6	0.93
BMI (kg/m^2)			
• Pre CR	30 ± 7	28 ± 5	
• Post CR	30 ± 7	27 ± 4	0.05
• Change	0 ± 1	0 ± 1	0.9
SBP (mmHg)			
• Pre CR	133 ± 18	125 ± 15	
• Post CR	121 ± 14	118 ± 14	0.33
• Change	-3 ± 17	-4 ± 14	0.69
DBP (mmHg)			
• Pre CR	76 ± 10	76 ± 9	
• Post CR	71 ± 9	70 ± 12	0.65
• Change	-2 ± 11	-2 ± 9	0.83
Cholesterol (mg/dl)			
• Pre CR	151 ± 39	161 ± 38	
• Post CR	157 ± 35	164 ± 42	0.43
• Change	13 ± 33	5 ± 23	0.27
6 MWD** (ft)			
• Pre CR	1394 (1145, 1648)	1460 (1295, 1595)	
• Post CR	1673 (1454,1865)	1648 (1485,1848)	0.87
• Change	+ 197 (121, 295)	+ 173 (125, 238)	0.42
• % Change	14%	12%	
EMW†			
• Pre CR	60 (1, 120)	75 (1, 130)	
• Post CR	160 (120, 240)	180 (120, 210)	0.55
• Change	+80 (40, 130)	+90 (45, 175)	0.44
• % Change	133%	120%	
GAD7‡			
• Pre CR	1 (0, 4)	2 (0, 3)	
• Post CR	1 (0, 3)	0 (0, 1)	0.15
• Change	0 (-2, 0)	-1 (-2, 0)	0.16
PHQ9§			
• Pre CR	3 (1, 6)	2 (1, 3)	
• Post CR	1 (0, 3)	1 (0, 3)	0.9
• Change	-1 (-3, 0)	-1 (-2, 0)	0.12
COOP††			
• Pre CR	18 (15, 22)	18 (15, 22)	
• Post CR	15 (13,19)	14 (12,17)	0.15
• Change	-2 (-4, 0)	− 3 (-5,-1)	0.24

	Surgical Aortic Valve N=94	Surgical Mitral Valve N=46	P Value*
Weight (lb)			
• Pre CR	204 ± 48	186 ± 50	
• Post CR	199 ± 44	178 ± 43	0.02
• Change	- 1 ± 7	-1 ± 6	0.93
BMI (kg/m^2)			
• Pre CR	30 ± 7	28 ± 5	
• Post CR	30 ± 7	27 ± 4	0.05
• Change	0 ± 1	0 ± 1	0.9
SBP (mmHg)			
• Pre CR	133 ± 18	125 ± 15	
• Post CR	121 ± 14	118 ± 14	0.33
• Change	-3 ± 17	-4 ± 14	0.69
DBP (mmHg)			
• Pre CR	76 ± 10	76 ± 9	
• Post CR	71 ± 9	70 ± 12	0.65
• Change	-2 ± 11	-2 ± 9	0.83
Cholesterol(mg/dl)			
• Pre CR	151 ± 39	161 ± 38	
• Post CR	157 ± 35	164 ± 42	0.43
• Change	13 ± 33	5 ± 23	0.27
6 MWD** (ft)			
• Pre CR	1394 (1145, 1648)	1460 (1295, 1595)	
• Post CR	1673 (1454,1865)	1648 (1485,1848)	0.87
• Change	+ 197 (121, 295)	+ 173 (125, 238)	0.42
• % Change	14%	12%	
EMW†			
• Pre CR	60 (1, 120)	75 (1, 130)	
• Post CR	160 (120, 240)	180 (120, 210)	0.55
• Change	+80 (40, 130)	+90 (45, 175)	0.44
• % Change	133%	120%	
GAD7‡			
• Pre CR	1 (0, 4)	2 (0, 3)	
• Post CR	1 (0, 3)	0 (0, 1)	0.15
• Change	0 (-2, 0)	-1 (-2, 0)	0.16
PHQ9§			
• Pre CR	3 (1, 6)	2 (1, 3)	
• Post CR	1 (0, 3)	1 (0, 3)	0.9
• Change	-1 (-3, 0)	-1 (-2, 0)	0.12
COOP††			
• Pre CR	18 (15, 22)	18 (15, 22)	
• Post CR	15 (13,19)	14 (12,17)	0.15
• Change	-2 (-4, 0)	− 3 (-5,-1)	0.24

*P value within group
** 6 Minutes walking distance
† Exercise minutes per week
‡ Anxiety scores
§ Depression scores
††Overall health quality

Table 3: Prediction model using Linear regression for delta 6MWD

Number of Observations = 91

Variables in Regression Model	Univariate analysis (95% CI)	P value	Multivariable analysis (95% CI)	P Value
Mitral Valve	-24.8 (-87.5, 38.0)	0.44	-27.8 (-91.3, 35.7)	0.39
Age	-0.9 (-3.3,1.4)	0.43	-2.7 (-5.5, -0.02)	0.048
6MWD*	-0.1 (-0.2, -0.02)	0.02	-0.2 (-0.3, -0.08)	<0.01
Gender	28.7 (-34.4, 91.8)	0.37	65.4 (-0.6, 131.4)	0.05
BMI*	-2.8 (-7.6, 2.1)	0.26	-4.9 (-9.9, 0.1)	0.06
CAD**	-27.3 (-103.3, 48.7)	0.48	-48.7 (-128.5, 31.2)	0.23
PHQ9*	2.8 (-3.3, 8.9)	0.36	5.5 (-6.2, 17.2)	0.37
EMW*	0.14 (-0.2, 0.5)	0.41	0.2 (-0.2, 0.5)	0.32
GAD7*	1.7 (-4.7, 8.1)	0.6	-4.4 (-16.7, 7.9)	0.48
COOP*	4.4 (-2.1, 10.9)	0.18	1.2 (-6.8, 9.1)	0.77

*Pre-Cardiac Rehab values

Supplemental Table 4
Clinical and demographics of total aortic valve and total mitral valve patients (N=161)

		Total Aortic Valve (N=115)	Total Mitral Valve (N=46)	P Value*
Age (years)		67 ± 13	64 ± 13	0.19
Female (% of total)		34 (30%)	19 (41%)	0.15
Weight (lbs.)				
• Pre CR		201 ± 48	186 ± 50	0.08
• Post CR		198 ± 45	177 ± 42	0.02
• Change		- 1 ± 7	-1 ± 6	0.96
Body Mass Index (kg/m^2)				
• Pre CR		30 ± 7	28 ± 5	0.04
• Post CR		30 ± 7	27 ± 4	0.02
• Change		0 ± 1	0 ± 1	0.79
Risk category				0.3
• Low		33 (29%)	12 (27%)	
• Medium		50 (44%)	15 (34%)	
• High		30 (27%)	17 (39%)	
ETT data	Baseline Heart Rate (beats/m)	71 ± 13	79 ± 12	<0.01
	Peak Heart Rate (beats/m)	119 ± 24	119 ± 24	0.97
	Baseline SBP (mmHg)	133 ± 18	125 ± 15	<0.01
	Baseline DBP (mmHg)	75 ± 10	76 ± 9	0.51
	Peak exercise SBP (mmHg)	152 ± 24	146 ± 22	0.14
	Peak exercise DBP (mmHg)	73 ± 11	73 ± 10	0.86
Risk Factors				
• Hypertension		102 (90%)	33 (73%)	<0.01
• Diabetes Mellitus		26 (23%)	2 (4%)	0.02
• Current smoker		17 (15%)	3 (7%)	0.15
• Hyperlipidemia		84 (74%)	26 (60%)	0.08
• Coronary Artery Disease		30 (26%)	5 (11%)	0.03
• Congestive Heart failure		9 (8%)	6 (13%)	0.3
Glycated Hemoglobin A1C (Patients with Diabetes = 28)		5.9 ± 0.9	5.6 ± 0.7	0.13
Total Cholesterol (mg/dl)		150 ± 41	161 ± 38	0.2
Ejection Fraction		58 ± 12	56 ± 12	0.44

Medication • β Blocker • Calcium Blocker • ACEi/ARB • Statin	90 (78%) 22 (19%) 41 (36%) 82 (71%)	35 (76%) 5 (11%) 12 (26%) 22 (48%)	0.76 0.2 0.24 <0.01
Exercise Test METS	6 ± 3	7 ± 3	0.17
Completed Cardiac Rehab	81 (73%)	35 (81%)	0.28
6 MWD(ft) • Pre CR • Post CR • Change • %Change	1344 (1085, 1598) 1592 (1400,1825) + 195 (116, 290) 14.5%	1460 (1295, 1595) 1648 (1485,1848) + 173 (125, 238) 12%	0.18 0.39 0.56
EMW† (minutes) • Pre CR • Post CR • Change • %Change	48 (1, 120) 160 (120, 225) +89 (40, 139) 185%	75 (1,130) 180 (120, 210) +90 (45, 175) 120%	0.26 0.55 0.47
GAD7‡ • Pre CR • Post CR • Change	2 (0,4) 1 (0, 3) 0 (-1, 0)	2 (0,3) 0 (0, 1) -1 (-2, 0)	0.89 0.16 0.08
PHQ9§ • Pre CR • Post CR • Change	3 (1, 6) 1 (0,3) -1 (-3,0)	2 (1,3) 1 (0,3) -1 (-2, 0)	0.19 0.92 0.26
COOP†† • Pre CR • Post CR • Change	18 (15, 22) 15 (14,19) -2 (-4, 0)	18 (15, 22) 14 (12,17) − 3 (-5,-1)	0.6 0.09 0.12

*P value comparing total mitral valve and total aortic valve patients (AVP and TAVR)
† Exercise minutes per week
** 6 Minutes walking distance
‡ Anxiety scores
§ Depression scores
††Overall health quality

Supplemental Table 5
Pre and Post Cardiac Rehabilitation values of patients with aortic valve subgroups (N=115)

	SAVP N=94	**TAVR N=21**	**P value***
Age	64 ± 12	79 ± 10	<0.01
Female	28 (30%)	6 (29%)	0.91
Weight (lb)			
• Pre CR	204 ± 48	188 ± 48	0.16
• Post CR	199 ± 44	195 ± 48	0.78
• Change	-1 ± 7	-2 ± 5	0.6
BMI (kg/m^2)			
• Pre CR	30 ± 7	31 ± 6	0.9
• Post CR	30 ± 7	31 ± 6	0.43
• Change	0 ± 1	0 ± 1	0.61
SBP (mmHg)			
• Pre CR	133 ± 18	135 ± 16	0.56
• Post CR	121 ± 14	125 ± 10	0.31
• Change	-3 ± 17	-10 ± 18	0.17
DBP (mmHg)			
• Pre CR	76 ± 10	70 ± 9	0.02
• Post CR	71 ± 9	64 ± 8	<0.01
• Change	-2 ± 11	-3 ± 9	0.95
Risk category			0.09
• Low	31 (34%)	2 (10%)	
• Medium	38 (41%)	12 (57%)	
• High	23 (25%)	7 (33%)	
Risk Factors			
• Hypertension	81 (88%)	21 (100%)	0.1
• DM	23 (25%)	3 (15%)	0.61
• Smoker	16 (18%)	1 (5%)	0.14
• Hyperlipidemia	67 (73%)	17 (81%)	0.44
• CAD	30 (32%)	0	<0.01
• CHF	7 (7%)	2 (10%)	0.75
Ejection Fraction	58 ± 12	58 ± 12	0.94
Medications			
• β Blocker	76 (81%)	14 (67%)	0.15
• Statins	65 (69%)	17 (81%)	0.28
• ACEi/ARBs	32 (34%)	9 (43%)	0.45
• CCBs	12 (13%)	10 (48%)	<0.01
Completed Cardiac Rehab	65 (71%)	16 (80%)	0.43
Exercise Test METS	7 ± 3	5 ± 3	0.02
6 MWD**(ft)			<0.01

	SAVP N=94	TAVR N=21	P value*
• Pre CR	1394 (1145,1648)	1088 (962,1330)	<0.01
• Post CR	1673 (1454,1865)	1284 (1043,1530)	0.37
• Change	+ 197 (121, 295)	+ 150 (68, 274)	
• %Change	14%	14%	
EMW†			
• Pre CR	60 (1,120)	1 (1,60)	0.09
• Post CR	160 (120, 240)	145 (90, 170)	0.06
• Change	+80 (40, 130)	+100 (40, 149)	0.66
GAD7‡			
• Pre CR	1 (0, 4)	3 (0, 4)	0.92
• Post CR	1 (0, 3)	1 (0, 2)	0.78
• Change	0 (-2, 0)	0 (-1, 1)	0.28
PHQ9§			
• Pre CR	3 (1, 6)	2 (1, 6)	0.49
• Post CR	1 (0, 3)	2 (0, 4)	0.54
• Change	-1 (-3,0)	0 (-1, 1)	0.08
COOP††			
• Pre CR	18 (15, 22)	20 (16, 22)	0.38
• Post CR	15 (13, 19)	18 (15, 21)	0.08
• Change	-2 (-4, 0)	− 2 (-2, 2)	0.12

*P value for trend
† Exercise minutes per week
** 6 Minutes walking distance
‡ Anxiety scores
§ Depression scores
††Overall health quality

Figure 1. Patients with aortic or mitral valve procedures enrolled in Cardiac Rehabilitation (CR)

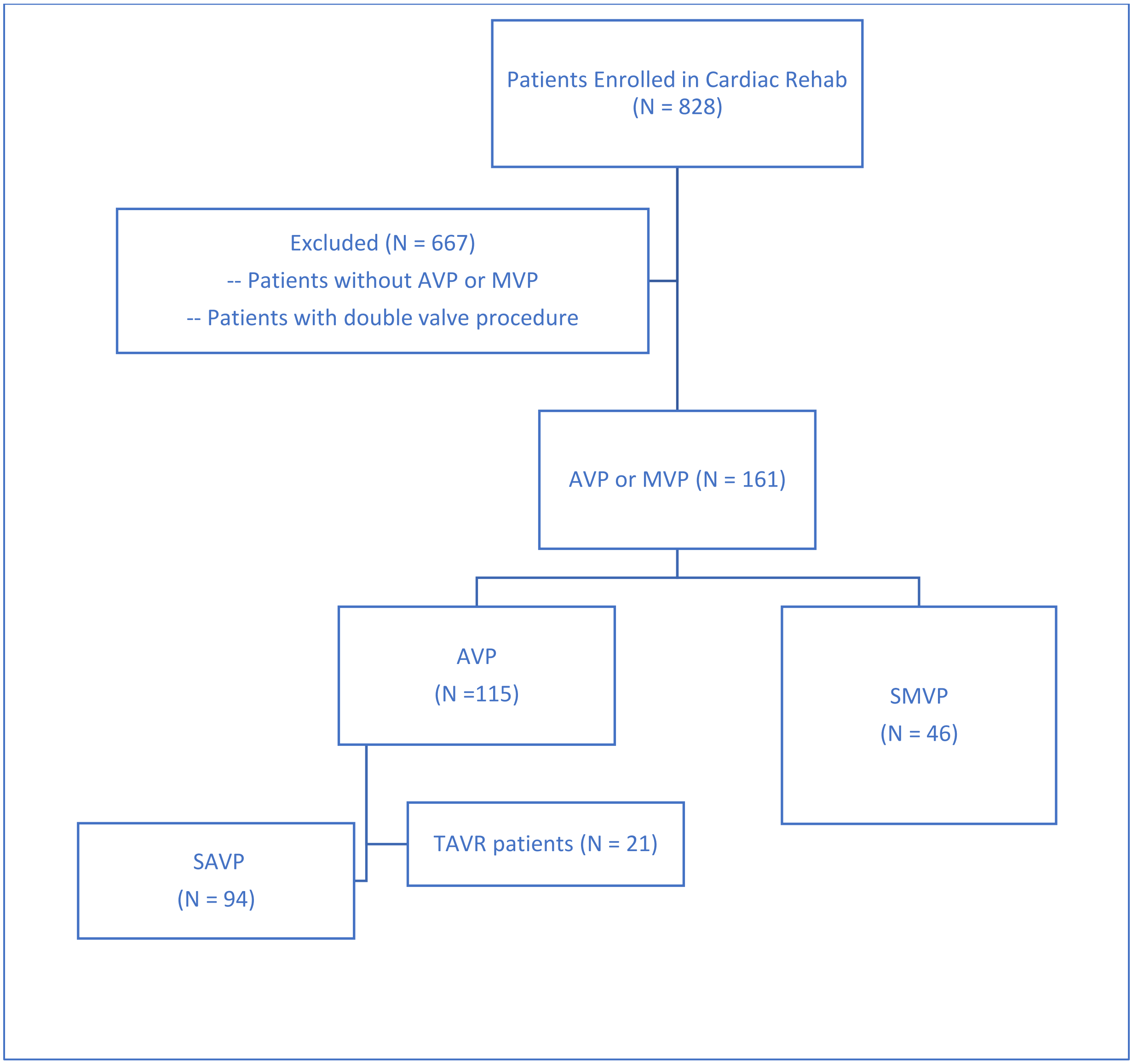
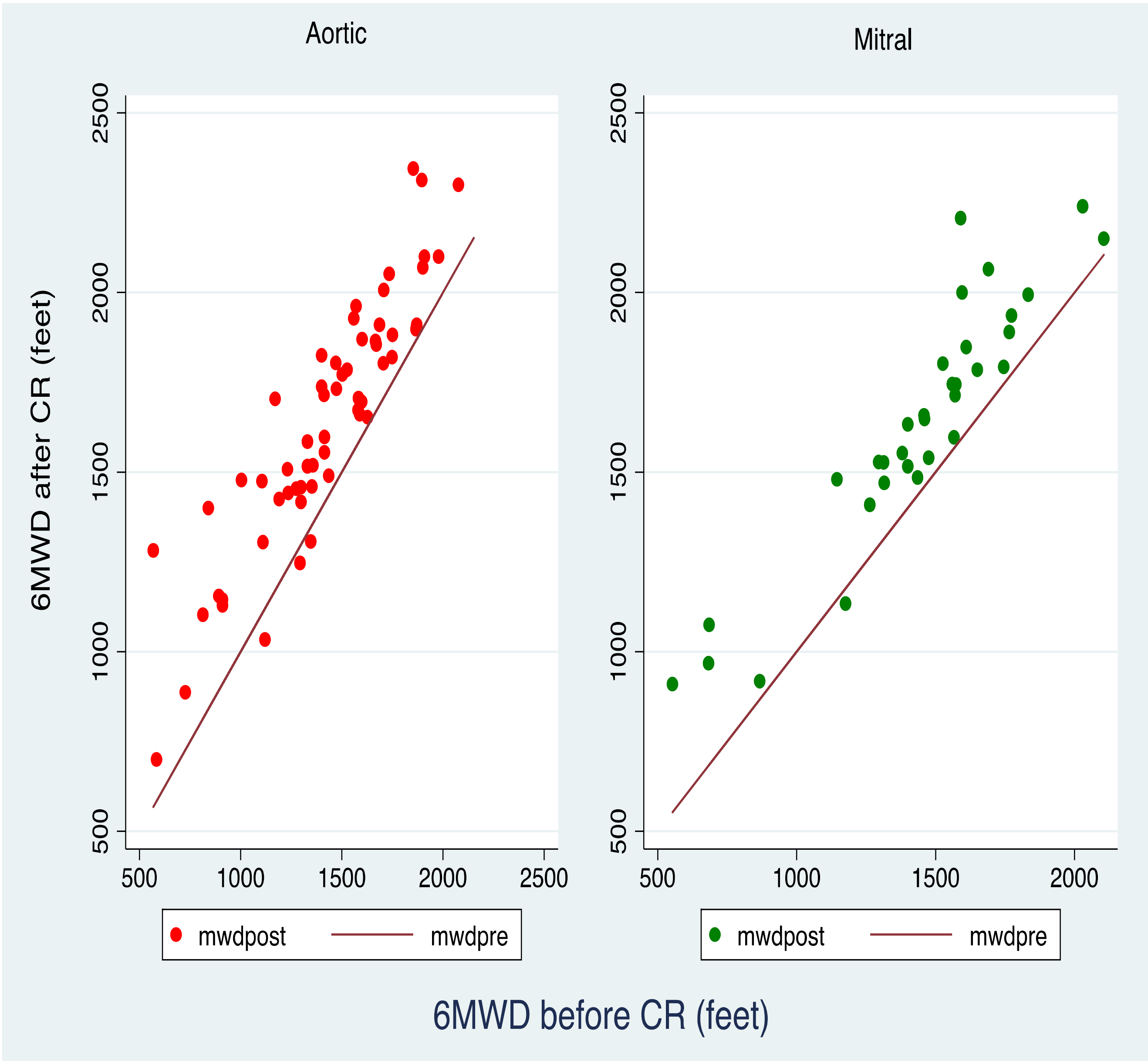


Figure 2. Six Minute Walk Distance before and after CR comparing SAVP and SMVP



Use of Guideline Directed Medical Therapy in Patients with Cardiovascular Disease Undergoing Cardiac Rehab

S. Hammad Jafri, M.D.[1,2]; Pavel Huschsa, M.B.B.S.[2]; Pranav Dorbala, B.S.[2]; Gisele Bousquet, M.S., R.N.[3]; Christine Lutfy, R.N.[3]; Jodi Klein, P.T.[3]; Lindsay Sonis, R.N.[3]; Donna Polk, M.D., M.P.H.[2]; Hicham Skali, M.D., M.Sc[2].

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1. Master of Medical Sciences in Clinical Investigation, Harvard Medical School, Boston, Massachusetts, USA.
2. Department of Cardiology, Brigham and Women's Hospital, Boston, Massachusetts, USA.
3. Cardiac Rehabilitation program, Brigham and Women's Hospital, Foxborough, MA

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*Corresponding Author
Hicham Skali, M.D.
Department of Medicine, Brigham and Women's Hospital
75 Francis Street
Boston, MA, 02115
Email: hskali@bwh.harvard.edu

ABSTRACT

Introduction:

Optimizing Guideline Directed medical therapy (GDMT) in Coronary Artery Disease (CAD) & Heart Failure (HF) patients is the key for recovery from the primary event as well as for prevention of further cardiovascular events. Cardiac Rehabilitation (CR) has shown improvements in secondary prevention but little is known about use of GDMT in this patient population.

Hypothesis:

The purpose of this retrospective cohort study is to examine the use of GDMT with CAD & HF patients undergoing CR versus patients not on GDMT. Also, to identify predictors of GDMT among patients enrolled in CR.

Methods:

CAD patients include Acute Myocardial Infarction (AMI), Percutaneous Coronary Intervention (PCI), Coronary Artery Bypass Grafting (CABG), and Angina. CAD GDMT is defined as patients taking all currently recommended medications (aspirin or antiplatelet, statins , beta blockers (BB) and ACEi/ARB if HF or DM). HF is defined as patients with HFrEF $\leq$ 40%. HF GDMT includes BB, spironolactone & either ACEi/ARB or Angiotensin Receptor Neprilysin Inhibitor (ARNI). Multivariable logistic regression was used to determine predictors of the GDMT.

Results:

The CAD group consisted of 612 patients, out of the 828 total, enrolled from January 2015 till December 2019. The only differences between the two groups were that patients on GDMT had less anxiety before CR (p=0.03), were more likely to have HTN, HLP, AMI and were less likely to have angina then patients not on GDMT. 466 (76%) patients were on complete GDMT, 577 (94%) were on 2/3 medications and 590 (96%) on 1/3 medication while 52/82 (63%) diabetes patients were on ACEi/ARBs. Between 2015- 2019, there were no changes in trend for GDMT or any other medications for CAD. In a multivariable model AMI, HTN, HLP and 6MWD pre-CR are seen to be better predictors of GDMT.

In the HF group (N=131), there were no baseline characteristic differences other than patients on GDMT were less likely to have HLP then those not on GDMT. 23/131 (18%) patients were on complete GDMT, 99 (76%) were on 2/3 medications and 128 (98%) were on 1/3 medication. During the years of 2015-2019, the use of ARNI, spironolactone & ACEi/ARBs has increased. In a multivariable model there are no predictors of GDMT.

Conclusions:

Among CAD patients, 24% were not on GDMT & BB was the least prescribed medication. Among HF patients, 82% were not on GDMT & spironolactone was the least prescribed medication. CR can provide the perfect opportunity to optimize GDMT in CAD and HF patients.

Introduction

Optimizing Guideline Directed Medical Therapy (GDMT) in patients with Coronary Artery Disease (CAD) & Heart Failure (HF) is key for recovery from the primary event as well as for prevention of further cardiovascular events. Patients with CAD not on GDMT have higher morbidity and mortality[1-3]. Exercise based Cardiac Rehabilitation (CR) programs have also shown improvements in quality of life and secondary prevention of cardiovascular events[4-5] however, little is known about the prevalence of GDMT in this patient population. CR can provide more than 20% reduction in cardiovascular mortality for CAD patients after completion of therapy[6]. Since most of the patients are enrolled in CR within a few weeks of diagnosis, CR can provide an excellent opportunity to assess prevalence of GDMT as well as monitor overall health during CR which can further improve morbidity and mortality.

We compared characteristics of patients on GDMT with patients not on GDMT. Also, we aimed to identify potential predictors of better GDMT in a patient population participating in CR.

Methods

Comprehensive data collection was performed on consecutive patients enrolled in the Brigham and Women’s Hospital CR program in Foxborough, MA. Patients on GDMT with CAD were compared to the patients not on GDMT enrolled in a 12-week CR outpatient program between January 2015 and December 2019.

Patients who were enrolled in CR with Percutaneous Coronary Intervention (PCI), Coronary Artery Bypass Grafting (CABG), Acute Myocardial Infarction (AMI) and Angina were classified under CAD category. Aspirin or antiplatelets, Beta Blockers (BB) and statins were included to assess prevalence of medications for GDMT in the CAD patient group. Medications like ACEi/ARBs were included in GDMT if patients had a diagnosis of HF, left ventricular systolic dysfunction (EF $\leq$ 40%), or diabetes.

The HF cohort included patients with an enrollment diagnosis of Heart Failure with reduced Ejection Fraction (HFrEF) or with Left Ventricular Systolic Dysfunction (LVSD) with EF $\leq$ 40%. Medications included for GDMT in HF patients were beta blockers, spironolactone and either ACEi/ARBs or Angiotensin Receptor Neprilysin inhibitors (ARNI). Prescribed medications were reviewed with the patient and recorded at time of enrollment in CR. A diagnosis of Hypertension (HTN), CAD, Diabetes Mellitus (DM) and Hyperlipidemia (HLP) were recorded at the point of entry to CR and smoking history was self-reported. Details about procedures like CABG and PCI were gathered retrospectively via chart review.

Overall health score was determined by COOP[7], depression by Geriatric Depression Scale (PHQ-9)[8] and anxiety by GAD-7[9] scores. Exercise capacity was assessed during exercise test prior to commencing CR. 6MWD (six minutes walking distance) was measured before CR. The study protocol was approved by the Internal Review Board at the Brigham and Women's hospital.

The exercise training program is similar to that performed at most rehabilitation programs around the United States. Generally, individuals exercise for 45 to 60 minutes per CR session on a variety of modalities including: treadmills, elliptical trainers and rowing, cycle and arm ergometers. Upper body strength training began 3-months post-operatively. All patients were encouraged to exercise aerobically on non-CR days.

Statistical Analysis

Values are presented as mean ± standard deviation, median with interquartile range, frequencies or percentages. For each condition (CAD or HF), the cohort was separated into 2 groups: GDMT and not on GDMT. T test and wilcoxon signed rank test was used to compare baseline variables between the groups. Univariate analysis was done to identify independent variables associated with prevalence while multivariable logistic regression was used to determine predictors of the better GDMT in CAD & CHF patients participating in CR. Variables included in the model are diagnosis of HTN, HLP, DM, smoking, CABG, PCI, AMI, angina, LVEF, weight pre-CR, 6MWD pre-CR, anxiety scores (GAD-7) and depression scores (PHQ-9) pre-CR. A level of significance of $P < 0.05$ was used for hypothesis testing. Statistical analyses were carried out using Stata statistical package (Stata 15.1).

Results

A total of 828 patients were enrolled in Cardiac Rehabilitation from January 2015 to December 2019. There were 612 patients identified with CAD and 466 (76%) patients were on GDMT. There were no difference in age, gender, weight, blood pressure, total cholesterol, HbA1c , exercise mets, CR completion, left ventricular ejection fraction and 6MWD among 2 groups.

Also, patients on GDMT were more likely to have HTN, HLP, AMI but less likely to have angina than patients not on GDMT (Table 1).

There were no differences in diabetes, smoking, CABG, PCI or HFrEF among the two groups. Patients on GDMT had less anxiety with GAD7 before CR (p=0.03). Patients on GDMT had lower baseline heart rate than patients not on GDMT (p=<0.01). There were no differences in 6MWD, PHQ-9 and COOP scores before CR in both groups.

Among patients with CAD, 466 (76%) were on all three GDMT (Aspirin or antiplatelets, BB and statins), 577 (94%) were on 2/3 medications and 590 (96%) were taking on 1/3 medication (Figure 1). For patients with DM and HFrEF or LVSD (N=82), 52 (63%) were on ACEi/ARBs (Table 2). In year-wise comparison from 2015 till 2019 for patients with CAD, there is no change in trend for use of GDMT or any other medication including aspirin, statin, BB or antiplatelets (Table 3). In a multivariable model 6MWD pre-CR, HTN, HLP and AMI are seen to be better predictors of GDMT in CAD patients (Table 4).

There were 131 patients in the HF cohort (diagnosis of HFrEF or LVSD), and only 23 patients were on appropriate HF GDMT. There were no baseline characteristic differences among patients on GDMT vs not on GDMT (Table 1). In this HF cohort, 23/131(18%) were on all 3 medications (BB, spironolactone and either ACEi/ARB or ARNI), 99 (76%) patients were on 2/3 medications and 128 (98%) patients were on a single medication (Table 5 & Figure 1). In year comparison from 2015 till 2019 for HF patients, use of neprilysin inhibitors, spironolactone &

ACEi/ARBs has increased (Table 6). In 2015 patients were only taking ACEi/ARB while in 2019, patients are now taking spironolactone, more ACEi/ARBs and combination of medications including new ones (neprilysin inhibitors). In a multivariable model, we could not identify predictors of GDMT in the HF cohort (Table 7).

Discussion

Our objective of this study was to assess prevalence of GDMT in CAD & HF patients and compare baseline characteristics of patients not on GDMT patients undergoing CR. We also assessed their year wise trend and attempted to identify predictors of GDMT for each condition. In our study, patients have no difference in baseline characteristics among two groups with HF and CAD. Overall, the prevalence of aspirin and statins were the highest with more than 90% of patients taking both medications, while BB were used by more than 80% of patients.

Our study patient population were seen to have a higher prevalence of medications than average patients without CR in previous studies with CAD, HF and HTN[10-13]. Our study has shown that prevalence is higher if patient is on single or two medications otherwise it is low for 3 or more medications. Also, prevalence of medications among patients with cardiovascular disease is higher in 2019 then in 2015.

In a recent study[14], GDMT was seen to be crucial for preventing progression of cardiovascular disease. While previous studies have shown importance of GDMT in patients with cardiovascular disease, there are no studies about prevalence of GDMT in patients undergoing

CR. Our study has shown that prevalence of medications is better among patients with cardiovascular diseases and prevalence goes up for single or two medications regardless of CAD, HF or DM. Aspirin and statins were the most prevalent medications taken, followed by BB in patients with CAD. Among HF patients, BB were the most used medications, followed by ACEi/ARBs, and spironolactone was the least used medication. It is unclear if it is side effect profile of medications like BB in case of CAD, or spironolactone in case of HF, more than once daily dosing or may be a combination of factors causing this difference, and this needs further research.

In previous studies multiple approaches have been successful to increase prevalence. Multifaceted approach where combination of provider (either physician, pharmacist, or nurse) follow-up is performed in person or by telephone, polypill concept with fixed dose combinations and monitoring with the use of text message are associated with improved prevalence[15]. Pharmacist supervised programs have shown better prevalence among patients with CAD, HF and DM[16]. Also use of smartphones, software applications, and telemedicine has the potential to further increase prevalence if used appropriately[17-21].

It is unclear if lifestyle changes or acute illness cause more prevalence to medical treatment in our group. It remains to be seen whether this prevalence is sustainable and predicts better clinical outcomes in long-term.

There are several limitations to our analysis. We reviewed prescriptions from patients at enrollment in cardiac rehabilitation and did not assess for adherence at beginning or throughout CR program. Medication potency or dosing were not analyzed. Specifically, high-potency statins for CAD or maximally tolerated dose for a BB or ACEi/ARB were not assessed. In addition, target effect of medications was not evaluated (target LDL, or heart rate for example). Moreover, potential reasons that would preclude prescription of GDMT medications were not accounted for. Specifically, we did not collect potential allergies or contraindications to medications, such as hyperkalemia, advanced chronic kidney disease or acute kidney injury for inhibitors of the renin-angiotensin-aldosterone system. It is possible that many patients in CAD group were motivated to be on GDMT as they did have a new diagnosis vs chronic diagnosis, however we did not have details of new vs chronic patients thus making it difficult to know the exact reason. Our study also has limitations as results are only from one Cardiac Rehabilitation center. The study design was observational and non-randomized thus has potential for known and unknown confounding. CR is utilized less, although it is the standard of care[22], limiting randomizing individuals to a non-exercising control group.

Conclusion

Among patients with CAD undergoing CR, 24% patients were not on optimal GDMT and BB was the least prescribed medication in this group. Among HF patients, 82% were not on GDMT and spironolactone was the least frequently prescribed medication. Use of ARNI & spironolactone has increased over the years. We need to assess whether GDMT is associated with better outcomes in patients undergoing CR. CR can provide the perfect opportunity to optimize medical treatment in patients with CAD or HF.

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Table 1: Clinical and demographic characteristics for patients undergoing CR

		CAD patients (N =612)			HF and LVSD patients (N=131)		
		On GDMT (N = 466)	Not on GDMT (N = 146)	P Value for trend	On GDMT (N = 23)	Not GDMT (N =108)	P Value for trend
Age (years)		65 ± 10	63 ± 11	0.12	62 ± 14	65 ± 13	0.21
Female (% of total)		98 (21%)	40 (27%)	0.11	3 (13%)	25 (23%)	0.28
Weight (lbs.)		195 ± 39	201 ± 44	0.1	203 ± 38	195 ± 43	0.39
Body Mass Index (kg/m^2)		30 ± 5	31 ± 6	0.07	30 ± 5	30 ± 5	0.97
Risk category				<0.01	NA	NA	NA
Low		172 (38%)	32 (25%)				
Medium		157 (34%)	38 (30%)				
High		130 (28%)	56 (44%)				
ETT data	Baseline Heart Rate (beats/m)	68 ± 12	72 ± 14	<0.01	70 ± 13	73 ± 13	0.4
	Peak Heart Rate(beats/m)	124 ± 22	126 ± 24	0.33	123 ± 26	117 ± 22	0.32
	Baseline SBP(mmHg)	127 ± 17	128 ± 18	0.66	115 ± 19	119 ± 18	0.35
	Baseline DBP(mmHg)	74 ± 10	73 ± 9	0.83	69 ± 9	71 ± 11	0.53
	Peak SBP(mmHg)	156 ± 24	158 ± 25	0.56	142 ± 26	138 ± 26	0.55
	Peak DBP(mmHg)	72 ± 10	72 ± 11	0.77	71 ± 10	70 ± 10	0.83
	Exercise Test METS	8 ± 3	8 ± 4	0.27	6 ± 3	6 ± 3	0.34
Risk Factors							
Hypertension		392 (85%)	90 (73%)	<0.01	21 (91%)	93 (88%)	0.63
Diabetes Mellitus		131 (28%)	36 (25%)	0.11	3 (13%)	27 (25%)	0.47
Current smoker		71 (15%)	20 (16%)	0.84	2 (9%)	14 (13%)	0.5
Hyperlipidemia		432 (93%)	106 (86%)	<0.01	14 (61%)	86 (81%)	0.04
CABG		173 (37%)	52 (36%)	0.74	NA	NA	NA
AMI		171 (37%)	39 (27%)	0.03	NA	NA	NA
PCI		238 (51%)	65 (45%)	0.17	NA	NA	NA
Angina		36 (8%)	22 (15%)	<0.01	NA	NA	NA
CAD		NA	NA	NA	7 (30%)	62 (57%)	0.02
HF (EF ≤40)		46 (10%)	23 (16%)	0.05	NA	NA	NA
Ejection Fraction		56 ± 10	55 ± 13	0.32	29 ± 8	32 ± 7	0.09
Glycated Hemoglobin A1c (N=391)		6.3 ± 3	6.4 ± 1	0.86	6 ± 1	7 ± 7	0.58
Total Cholesterol(mg/dl)		139 ± 41	143 ± 34	0.42	156 ± 40	139 ± 34	0.06
Completed Cardiac Rehab (% of total)		355 (79%)	92 (74%)	0.18	13 (81%)	75 (71%)	0.41
6 MWD (ft) **		1511	1465	0.06	1505	1325	0.04

	(1275,1750)	(1078,1746)		(1286, 1701)	(1084, 1570)	
GAD7!‡	2 (0,5)	3 (1,7)	0.03	2 (0, 5)	2 (0, 7)	0.22
PHQ9!!§	3 (1, 6)	3 (1,6)	0.59	4 (1, 6)	3 (1, 6)	0.81
COOP††	19 (15, 22)	19 (16, 23)	0.1	20 (16, 23)	20 (17, 24)	0.62

*P value comparing Aortic and Mitral group
**6 Minutes walking distance
† Exercise Minutes per week
‡ Anxiety scores
§ Depression scores
†† Overall health quality

Table 2
Number of medications among Cardiac Rehab patients with CAD (N = 612)

	GDMT (N=466)	**Not on GDMT (N=146)**
Aspirin or antiplatelets	466 (100%)	110 (75%)
B-Blockers	466 (100%)	48 (33%)
Statins	466 (100%)	94 (64%)
ACEi/ARBs (N=82)*	52 (100%)	6 (20%)

*Patients with DM and HFrEF

Table 3
Number of medications among CAD patients by year undergoing Cardiac Rehabilitation

	2015 (CAD=88)	2016 (CAD=100)	2017 (CAD=118)	2018 (CAD=147)	2019 (CAD=159)	P-Value for trend	Total Patients (N=612*)
GDMT	61 (69%)	77 (77%)	92 (78%)	112 (76%)	124 (78%)	0.24	466 (76%)
Aspirin or Antiplatelet	84 (96%)	95 (95%)	116 (98%)	136 (93%)	145 (91%)	0.07	576 (94%)
Statin	76 (86%)	91 (91%)	114 (97%)	135 (92%)	144 (91%)	0.46	560 (92%)
B-Blocker	69 (78%)	88 (88%)	103 (87%)	121 (82%)	133 (84%)	0.86	514 (84%)
ACEi/ARB**	5 (100%)	10 (83%)	15 (63%)	16 (64%)	12 (75%)	0.32	58 (71%)

*Except ACE/ARB group where N=82
**For patients with DM and HFrEF

Table 4
Predictors of Guideline directed medical therapy in patients with CAD (N=612)

Variables in Regression Model	Univariate analysis OR (95% CI)	P value	Multivariable analysis OR (95% CI)	P Value
Age	1.0 (0.9, 1.0)	0.12	1.0 (0.99, 1.04)	0.07
Gender	1.4 (0.9, 2.2)	0.1	1.1 (0.7, 1.8)	0.7
BMI*	0.9 (0.9, 1.0)	0.07	NA	
CABG	1.1 (0.7, 1.6)	0.7	NA	
AMI	1.6 (1.1, 2.4)	0.03	2.0 (1.2, 3.4)	<0.01
PCI	1.3 (0.9, 1.9)	0.19	NA	
Angina	0.5 (0.3, 0.8)	<0.01	0.7 (0.3, 1.4)	0.28
HTN	2.1 (1.3, 2.3)	<0.01	2.3 (1.3, 4.0)	<0.01
Diabetes	1.1 (0.9, 1.3)	0.3	NA	
HLP	2.4 (1.3, 4.4)	<0.01	2.7 (1.3, 5.6)	<0.01
Smoking	0.9 (0.6, 1.6)	0.8	NA	
6MWD*	1.01 (1.01, 1.02)	0.02	1.01 (1.01, 1.02)	<0.01
PHQ9*	0.9 (0.9, 1.1)	0.4	NA	
GAD7*	0.9 (0.9, 0.9)	0.04	1.0 (0.9, 1.0)	0.1

Table 5
Number of medications among Cardiac Rehab patients with HFrEF (N = 131)

	On GDMT for HFrEF (N=23/131)	Not on GDMT for HFrEF (N=108/131)
B Blockers	23 (100%)	99 (92%)
ACEi/ARBs or ARNI	23 (100%)	77 (71%)
Spironolactone	23 (100%)	5 (5%)
ACEi/ARBs	16 (100%)	73 (68%)
ARNI (N=13)	8 (62%)	5 (38%)

*Patients with HFrEF with BB, spirinolactone and either ACEi/ARB or ARNI

Table 6
HF medications by year

	2015 (HF=10)	2016 (HF=18)	2017 (HF=38)	2018 (HF=35)	2019 (HF=30)	P-Value for trend	Total Patients (N=131)
GDMT	0 (0%)	3 (17%)	6 (16%)	4 (11%)	10 (33%)	0.04	23 (18%)
B-Blocker	8 (80%)	18 (100%)	36 (95%)	31 (89%)	29 (97%)	0.58	122 (93%)
ACEi/ARB or ARNI*	9 (90%)	15 (83%)	29 (76%)	23 (66%)	24 (80%)	0.35	100 (76%)
Spirinolactone	0 (0%)	4 (22%)	7 (18%)	6 (17%)	11 (37%)	0.04	28 (21%)
ACEi/ARB	9 (90%)	15 (83%)	27 (71%)	21 (60%)	17 (57%)	<0.01	89 (68%)
ARNI*	0 (0%)	0 (0%)	2 (5%)	3 (9%)	8 (27%)	<0.01	13 (10%)

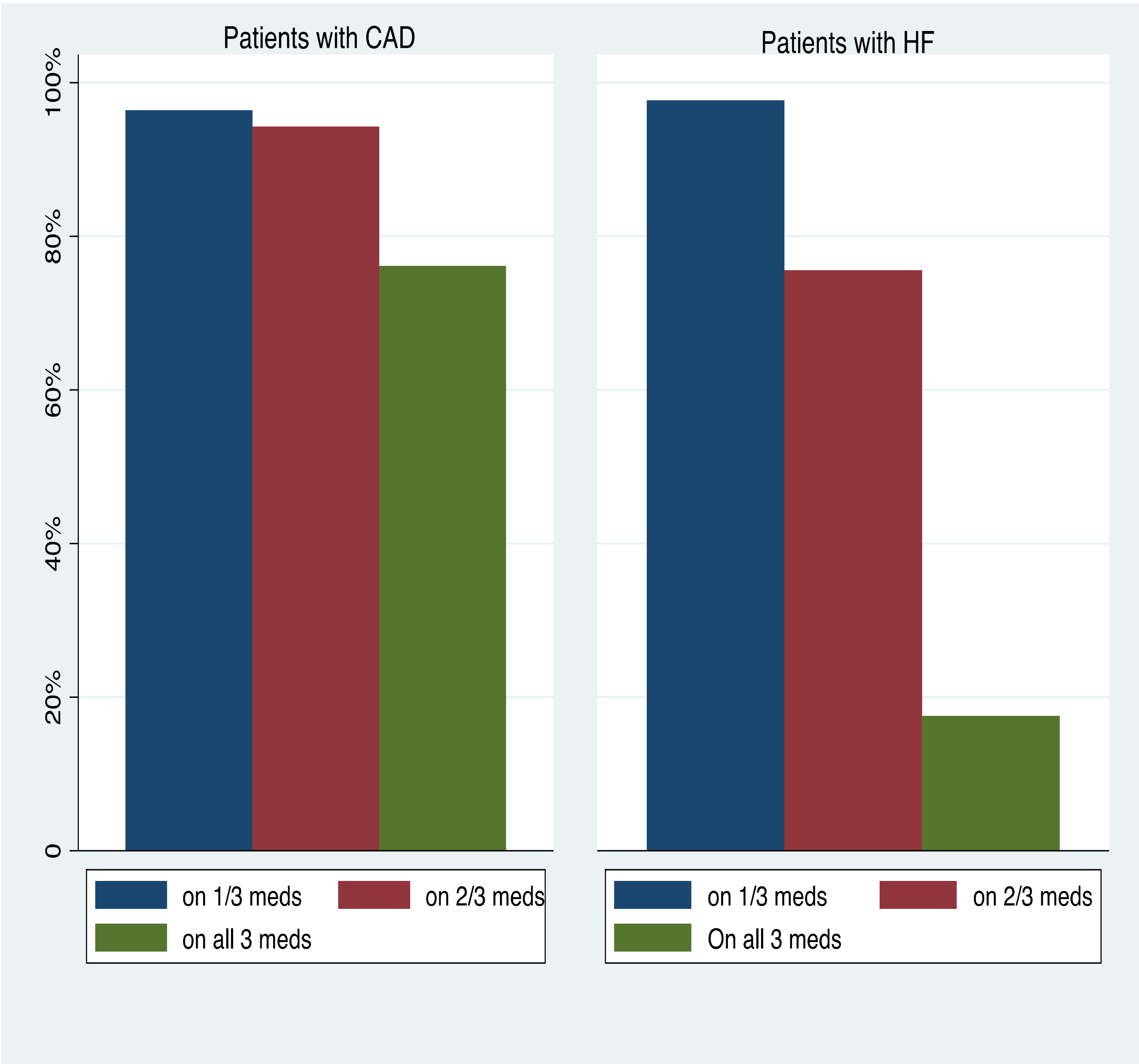
*Angiotensin receptor neprilysin inhibitor

Table 7
Predictors of GDMT in HF patients (N=131)

Variables in Regression Model	Univariate analysis OR (95% CI)	P value	Multivariable analysis OR (95% CI)	P Value
Age	0.9 (0.9,1.0)	0.21	0.9 (0.9, 1.0)	0.75
Gender	2.0 (0.5, 7.3)	0.29	3.8 (0.6, 22.4)	0.14
BMI*	0.9 (0.9, 1.1)	0.97	1.0 (0.9, 1.1)	0.79
LVEF**	0.9 (0.9, 1.0)	0.09	0.9 (0.9, 1.1)	0.48
CAD	0.3 (0.1, 0.9)	0.02	0.3 (0.1, 1.1)	0.07
HTN	1.5 (0.3, 7.0)	0.63	1.6 (0.2,11.2)	0.63
Diabetes	0.7 (0.5, 1.1)	0.17	0.7 (0.4, 1.1)	0.12
HLP	0.4 (0.1, 0.9)	0.04	0.7 (0.2, 2.6)	0.58
Smoking	0.6 (0.1, 3.0)	0.55	0.7 (0.1, 4.5)	0.79
6MWD*	1.0 (0.9, 1.0)	0.06	1.0 (0.9, 1.0)	0.33
PHQ9*	0.9 (0.9, 1.1)	0.74	1.0 (0.9, 1.2)	0.97
GAD7*	0.9 (0.8, 1.1)	0.28	1.0 (0.8, 1.2)	0.73

*Pre-Cardiac Rehab values
** Left ventricular ejection fraction

Figure 1.
Use of medications among patients with CAD and HF undergoing Cardiac Rehab



Summary of paper 1 and paper 2 conclusions

Our results showed improvement in physical as well as psychological well-being after completion of cardiac rehabilitation in both groups. Cardiac rehabilitation is beneficial for patients after mitral valve procedure as it shows similar improvements in physical activity between when compared to patients after aortic valve procedure. While procedure by itself improves increases exercise capacity in this patient population, cardiac rehabilitation can provide ideal opportunity to further maximize it. Closer monitoring of patient`s vitals, labs and overall condition can provide cardiac rehabilitation team help making decisions precisely to maximize benefits. While clinical trials cannot be done as cardiac rehabilitation is standard of care now, however larger observational studies are needed to further confirm our findings. in the meantime, patients after mitral valve procedure should continue to be encouraged to participate in cardiac rehabilitation.

Prevalence of guideline directed medical therapy in our study is better for patients with coronary artery disease and congestive heart failure patients without cardiac rehabilitation. Among patients undergoing cardiac rehabilitation almost 1/4 patients with coronary artery disease were not on optimal guideline directed medical therapy while 4/5 patients with congestive heart failure not on guideline directed medical therapy. Beta blockers & spironolactone was the least prescribed medications in patients with coronary artery disease & congestive heart failure undergoing cardiac rehabilitation respectively. Use of newer medications especially for patients with congestive heart failure have not only improved outcomes but also increased prevalence of medications among this patient population. We need to assess whether guideline directed medical therapy can be further improved using cardiac rehabilitation as effective tool as it can not only provide direct interaction but also monitoring closely after immediate diagnosis. Cardiac rehabilitation can also provide opportunity for counselling on a regular basis which is very helpful in increasing compliance and adherence.

Discussion and perspectives

Our studies provided important information about patients with cardiovascular diseases undergoing cardiac rehabilitation. It shows that cardiac rehabilitation is not only essential for immediate post diagnosis for recovery but also crucial for prevention of further cardiovascular diseases.

Our studies were retrospective from one cardiac rehabilitation center and since cardiac rehabilitation is standard of care so randomized clinical trials cannot be done, however large multicenter retrospective studies can provide further details and confirm our results.

Our limitation for 2nd study was that we reviewed prescriptions from patients at enrollment in cardiac rehabilitation and don't know exact adherence. Also, we don't know potency or exact dosing of medications like high dose statins required by patients with heart disease. It is not known the exact effects from these medications like change in cholesterol or heart rate from taking these medications. In last and not the least it is also unknown what are contraindications of medications patients were not prescribed. These problems can be managed easily by addressing medications not only on entry but also after completing cardiac rehabilitation and if possible, with each session.

Some of the key components required for guideline directed medical therapy for heart failure patients were not available like creatinine for kidney function and lab markers like potassium. Although cardiac rehabilitation protocol usually doesn`t gather these labs, however it can be collected as additional labs for further improvement of patients with heart failure to monitor heart failure progress and improve their outcomes.

As Medicare has approved cardiac rehabilitation since 2017 for patients after certain cardiac disease, however there are still many challenges faced by patients to participate in it. Cardiac rehabilitation sessions are 3 times weekly thus making it difficult for some working patients to take time off while others have issues with transportation. These challenges can be handled with proper coordination and hopefully can increase further participation.

As prevalence of patients undergoing cardiac rehabilitation is increasing more benefits will continue to emerge and tools will be identified for further decreasing morbidity and mortality.