International Journal of Medicine
pISSN 1468-3814 | eISSN 2667-7008
https://theinternationalmedicine.com/

Original Research Article *DOI: 10.61336/im/26-1-19*

Optimization of Target Dose Medical Therapy in Patients with Systolic Heart Failure: A Combined Retrospective and Prospective Observational Study

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Received: **November 25, 2025**
Revised: **January 01, 2026**
Accepted: **January 18, 2026**
Published: **January 29, 2026**

Abstract

Background: Heart failure with reduced ejection fraction remains associated with high morbidity and mortality despite GDMT (Guideline-Directed Medical Therapy). Although beta-blockers and RAAS (Renin–Angiotensin–Aldosterone System) inhibitors significantly improve outcomes, real-world data show suboptimal achievement of target doses. This study aimed to evaluate the percentage of patients achieving various quartiles of target doses of BB and RAAS inhibitors and to assess their impact on mortality and heart failure admissions. ***Methods:*** This was a single-centre combined retrospective and prospective observational study conducted from August 2017 to August 2019. A total of 324 patients with left ventricular ejection fraction ≤35% were enrolled and followed for a minimum of 12 months. Patients were categorized into five groups (A, B1, B2, B3, C) based on the percentage of target dose achieved for BB and RAAS inhibitors. Dose optimization was attempted systematically, and outcomes, including mortality and HF admissions, were recorded. Statistical analysis was performed using SPSS version 15.0, with $p<0.05$ considered significant. ***Results:*** The study population was predominantly male (70.1%) with ischemic cardiomyopathy (85.7%). At baseline, 76% of patients were in the lowest dose group (Group A), which reduced to 36% at 12 months following systematic uptitration. Approximately 23.8% achieved >50% target dose of either BB or RAAS inhibitors, while only 5.25% achieved >50% target dose of both drug classes. Mortality was significantly lower in Group B2 (high BB dose, lower RAAS dose) compared to Group B3 (moderate doses of both) (11.5% vs. 27.4%, p=0.019). HF admissions were too few for meaningful analysis ***Conclusion:*** Systematic dose uptitration significantly increases the achievement of higher GDMT doses in HFrEF (Heart failure with reduced Ejection Fraction) patients. Higher beta-blocker target dosing was associated with reduced one-year mortality, suggesting that beta-blocker optimization plays a crucial role in improving survival outcomes.

Keywords: Heart Failure, HFrEF, Beta-Blockers, RAAS Inhibitors, Target Dose, Mortality, Guideline-Directed Medical Therapy.

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INTRODUCTION

Heart failure is a complex clinical syndrome characterized by the inability of the heart to maintain adequate circulation due to structural and/or functional (systolic or diastolic) abnormalities.[1] It may result from any cardiac disorder that impairs ventricular filling or ejection of blood and remains primarily a clinical diagnosis supported by investigations such as chest radiography, electrocardiography, and echocardiography.[2] HF arises from structural and functional myocardial defects that compromise ventricular performance.[3] Although reduced left ventricular systolic function is the most common cause, abnormalities of the pericardium, myocardium, endocardium, heart valves, or great vessels may also contribute.[1] Pathogenic mechanisms include hemodynamic overload, ischemia-related dysfunction, ventricular remodelling, excessive neurohormonal activation, altered calcium handling, extracellular matrix changes, apoptosis, and genetic factors.[2]

HF may be classified as left, right, or biventricular, and as acute or chronic. Clinically, it is categorized into HFpEF (Heart Failure with preserved Ejection Fraction) and HFrEF (Heart Failure with reduced Ejection Fraction). HFpEF, commonly seen in elderly females, is characterized by an ejection fraction >50%, normal ventricular cavity size, and increased wall stiffness.[3]

HF is associated with significant morbidity, mortality, and reduced quality of life, imposing a substantial burden on healthcare systems.[3] One-year mortality following hospitalization ranges from 10% to 30%,[4] and median survival after diagnosis is less than four years.[5] Patients typically present with dyspnea, orthopnea,

paroxysmal nocturnal dyspnea, fatigue, and peripheral edema.[6,7]

Therapeutic advances have demonstrated that ACE (Angiotensin-Converting Enzyme) inhibitors, beta-blockers, and MRAs (Mineralocorticoid Receptor Antagonists) improve clinical outcomes when titrated to guideline-recommended doses.[8] However, in routine practice, many patients fail to achieve target doses, and prognosis remains poor.[9] Moreover, real-world populations often differ from clinical trial cohorts, raising concerns about treatment optimization, particularly in HFpEF. In such settings, well-designed observational studies may provide valuable insights into therapeutic effectiveness.[10]

AIMS AND OBJECTIVES

The study aims to evaluate the effect of target-dose medical therapy using a combination of beta-blockers and RAAS inhibitor drugs (MRA + ACEI/ARB/ARNI) in patients with systolic heart failure. The primary objective was to determine the percentage of patients receiving each quartile of the target dose (<25%, 25–<50%, 50–<75%, and >75%) of BB and RAAS inhibitor therapy. The secondary objectives were to compare heart failure admission plus mortality, HF admissions alone, and mortality alone among patients receiving different quartiles of the target dose in order to assess the impact of dose optimization on clinical outcomes.

MATERIALS AND METHODS

Study Design

This was a single-centre, combined retrospective and prospective observational study conducted among patients with heart failure enrolled in a dedicated heart failure registry from August 2017 to August 2019, with a total enrolment period of 49 months. All eligible patients were followed for a minimum duration of 12 months after enrolment. The primary objective of the study was to determine the percentage of patients achieving different dose ranges of the target dose of the study medications during the follow-up period.

Inclusion and Exclusion Criteria

Patients were included in the study if they had a LVEF (Left Ventricular Ejection Fraction) ≤35%. Patients were excluded if they had experienced an acute coronary syndrome within the previous one month, had undergone revascularization in the last one month, were younger than 18 years of age, did not provide consent, or were receiving medications not evaluated in established heart failure clinical trials.

Sample Size Calculation

At the time of initiation of this study, there had been no study in literature describing a longitudinal observation of heart failure patients receiving a particular dose category of the combination of BB and ABs. Greene S J et al., made a single-point cross-sectional observation of the percentage of patients with heart failure receiving the target dose or less than the target dose each of the following drugs independently: BB/ ACE-I/ARB/ARNI.

A calculation based on this study would be:

Primary variable: Percentage of patients who got the target dose of beta blockers

Null Hypothesis H0: Percentage = 27.5% (Ref. Greene SJ et al.)

H1: Anticipated Percentage = 34%

Sample Size = 426,

Power = 90%, Alpha = 0.05, Statistical test: Z test for binomial proportion.[11]

As this study classifies patients as those receiving the TD of both BB and AB, the differences are likely to be larger, and the required sample size, therefore, smaller.

Data Collection Procedure

The data collection procedure involved reviewing the medical records of all patients attending the cardiology department during the enrolment period to identify those diagnosed with heart failure and meeting eligibility criteria. Eligible patients were enrolled in a dedicated heart failure registry and followed up either telephonically or through in-person visits at 3, 6, and 12 months. At each visit, clinical details, including heart rate, blood pressure, echocardiographic findings, laboratory values, and medications, were recorded. Doses of beta-blockers and RAAS inhibitors were systematically up-titrated when feasible, documented at each time point, and expressed as a percentage of the predefined target dose. Patients were categorized into dose-based groups for analysis, and outcomes, including heart failure admissions and mortality, were recorded during follow-up.

Statistical Analysis

Statistical analysis was performed using SPSS version 15.0 (Statistical Package for the Social Sciences, Version 15.0). Continuous variables with normal distribution were expressed as mean ± standard deviation (SD) along with sample size (N), while non-normally distributed data were presented as median and range. Categorical variables were summarized as frequencies and percentages. Comparison of means between two groups for normally distributed numerical data was performed using the Student's unpaired t-test. The Fisher's Exact test was used to compare proportions between categorical variables. All statistical tests were two-tailed, and a p-value of <0.05 was considered statistically significant.

RESULTS

Variable	Category	Number (n)	Percentage (%)
Sex	Male	227	70.1
	Female	97	29.9
Age (in years)	30–40	7	2.2
	40–50	27	8.3
	50–60	74	22.8
	60–70	99	30.6
	70–80	79	24.4
	>80	38	11.7
Etiology	ICMP	240	85.7
	NICMP	40	14.3
Hypertension	Yes	162	59.1
Diabetes	Yes	204	69.9
Rhythm	NSR	292	92.1
	AF	25	7.9
QRS Duration	<120 ms	248	77.5
	>120 ms	72	22.5
NYHA Class	I	2	0.6
	II	120	37.0
	III	188	58.0
	IV	14	4.3

Table 1: Baseline Demographic and Clinical Characteristics (N = 324)

Table 1 illustrates that the majority of patients were elderly males with ischemic cardiomyopathy. Most patients were in NYHA Class II–III and had a high prevalence of diabetes and hypertension.

Target Dose (%)	Baseline n (%)	12 Months n (%)
0–15%	13%	5%
15–30%	37%	29.4%
31–50%	35.2%	31.3%
51–75%	4.6%	10.3%
76–100%	9.8%	24.3%

Table 2: Distribution of Patients by Target Dose Quartiles (Baseline vs 12 Months)

Table 2 shows significant improvement in dose optimization over 12 months, with a reduction in the low-dose group and a marked increase in patients achieving >50% of the target dose.

Time Point	Group A n (%)	Group B1 n (%)	p-value
Baseline	39 (76.5%)	12 (23.5%)	—
3 Months	16 (43.2%)	21 (56.8%)	0.0014
6 Months	19 (44.2%)	24 (55.8%)	0.001
12 Months	14 (35.9%)	25 (64.1%)	0.0001

Table 3: Group Distribution (A v.s B1) Over Time

Table 3 demonstrates a significant reduction in Group A (low dose) and an increase in Group B1 after systematic uptitration.

Time Point	Group A n (%)	Group B2 n (%)	p-value
Baseline	39 (61.9%)	24 (32.1%)	—
12 Months	14 (21.2%)	52 (78.8%)	<0.001

Table 4: Group Distribution (A vs. B2) Over Time

Table 4 shows a statistically significant shift from low-dose Group A to high beta-blocker dose Group B2 over time.

Time Point	Group A n (%)	Group C n (%)	p-value
Baseline	39 (88.6%)	5 (11.4%)	—
12 Months	14 (45.2%)	17 (54.8%)	<0.001

Table 5: Group Distribution (A vs C) Over Time

Table 5 illustrates a gradual increase in patients achieving high doses of both BB and RAAS inhibitors (Group C), though numbers remained relatively small.

Group	Mortality n (%)	Non-Mortality n (%)	p-value
B2	6 (11.5%)	46 (88.5%)	0.019
B3	45 (27.4%)	119 (72.6%)	

Table 6: Mortality Comparison between Groups B2 and B3

Table 6 shows significantly lower mortality in Group B2 (high BB dose) compared to Group B3 (moderate doses of both drugs).

Variable	B2	B3	p-value
ICMP (%)	83.1	94.7	0.185
AF (%)	9.3	4.2	0.399
QRS >120ms (%)	21.1	33.3	0.173
NYHA (Significant)	—	—	<0.001
Creatinine >2 (%)	13.7	16.7	0.695
Mean EF (%)	29.7 ± 5.8	29.5 ± 5.1	0.845

Table 7: Risk Factor Comparison between B2 and B3

Table 7 indicates that, except for NYHA class, no other baseline variables differed significantly between B2 and B3 groups, suggesting the mortality benefit in B2 was likely related to the higher beta-blockers dose.

DISCUSSION

This retrospective cohort study of 324 patients with systolic heart failure examined the proportion of patients receiving each quartile of the target dose for beta blockers and RAAS inhibitors (ACEI/ARB/ARNI + MRA) between January 2016 and December 2018. The cohort was predominantly male with ischaemic HFrEF (85.7%), approximately 70% were diabetic, and 95% were in NYHA Class II–III.

Dose Distribution and Up-titration

At baseline, most patients received sub-target doses: 13% were in the 0–15% group, 37% in the 15–30% group, and 35.2% in the 31–50% group; only 4.6% and 9.8% achieved 51–75% and 76–100% of the target dose, respectively. A further 12.3% were not on either drug class at enrolment. At 12-month follow-up, meaningful up-titration was evident: the proportion at ≥76% of target dose more than doubled (9.8% → 24.3%), while those in the lowest tier fell from 13% to 5%. Among patients initially below 15% of the target dose, 40% successfully stepped up by one year. Pair wise intergroup comparisons confirmed statistically significant increases in GDMT dosing at 3, 6, and 12 months, consistent with findings reported by Joseph et al.[12]

Comparison with Published Data

Joseph et al.,[12] in a retrospective study from a tertiary care centre in southern India, categorized HF patients into four dose-range arms for each drug class separately. For beta blockers, 55% were in the 0–25% group at baseline, improving to 21% in the ≥76% group at one year. For ACEI/ARBs, 44% reached the ≥76% tier at follow-up. Our data are broadly concordant; however, unlike that study, we assessed combined target dose across drug classes and correlated dose groups with mortality outcomes.

Landmark randomized trials achieved high individual target dose rates under controlled conditions - 42% in CIBIS-II,[13] 80% in the U.S. Carvedilol HF Study,[14] and 64% in MERIT-HF[15]- yet real-world registries show a stark contrast. OPTIMIZE-HF[16] found mean beta-blocker doses below 50% of the target, with fewer than 10% achieving the target dose at discharge. COHERE[17] reported only 41% reaching the carvedilol 25 mg twice-daily dose. Contemporary trials show similar underachievement: approximately 50%, 30%, and 25% of patients reached beta-blocker targets in HF-ACTION, SHIFT,[18] and CIBIS-ELD,[19] respectively. These data consistently demonstrate a gap between efficacy trial results and routine clinical practice.

The CHAMP-HF Registry[20] found that among patients eligible for all three drug classes, only 22.1% were simultaneously prescribed any dose of ACEI/ARB/ARNI, beta blocker, and MRA - and a mere 1.1% received target doses of all three. This underscores the case for trials that evaluate **combined** rather than individual target dose strategies.

Target Dose versus Target Heart Rate

Beta-blocker–mediated heart rate reduction decreases myocardial oxygen demand and improves mechanical efficiency-benefits abolished when HR is held constant by atrial pacing.[21] Pacing at 80 versus 60 beats/min attenuated the beneficial effects of beta-blockade on left ventricular volume and systolic function.[22] Notably, a meta-analysis demonstrated that achieving a low target HR-regardless of dose prescribed - was an independent determinant of survival in HFrEF patients in sinus rhythm.[23] Eriksen-Volnes et al.,[24] analyzing 2,689 patients from the Norwegian Heart Failure Registry, confirmed that HR ≥70 bpm was associated with worse outcomes, suggesting HR may be a more clinically meaningful target than absolute drug dose. Heart rate was not recorded at follow-up in the present study, and this question could therefore not be addressed.

Mortality Benefit with Combined Target Dose Therapy

Twelve-month mortality was compared across all five dose groups using the chi-square test. The primary mortality finding was a significant difference between Group B2 (beta blocker ≥50% target + RAAS inhibitor <50% target; mortality 11.5%) and Group B3 (both drugs at 15–50% target; mortality 27.4%) (p = 0.019). This indicates that prioritizing beta blocker dose over RAAS inhibitor dose confers a clinically meaningful survival advantage. Mortality in Group B1 (RAAS inhibitor ≥50% + Beta Blocker <50%) was 20%, not significantly different from Group B2, likely due to small group size. Group C (high dose of both agents) was expected to show the greatest benefit, but insufficient numbers precluded statistical analysis.

To assess whether the B2–B3 mortality difference was confounded by baseline characteristics, risk factors were compared (Table 1). Of the variables examined - etiology, rhythm, QRS duration, NYHA class, creatinine, and ejection fraction - only NYHA class differed significantly (p <0.001): Group B2 contained more NYHA Class III patients (61.3% vs. 20.8%), yet still demonstrated lower mortality, consistent with a dominant protective effect of higher beta blocker dosing even in more symptomatic patients. The RAAS inhibitor dose appeared to be a limiting factor for beta blocker up-titration, possibly due to haemodynamic effects. Taken together, these findings suggest that in GDMT for HFrEF, mortality is predominantly influenced by Beta Blocker dose achievement.

Variable		Mortality, n (%)		p-value
		Group B2	Group B3	
Etiology	ICMP	152 (83.1%)	18 (94.7%)	0.185
	NICMP	31 (16.9%)	1 (5.3%)	
Rhythm	AF	19 (9.3%)	1 (4.2%)	0.399
	NSR	185 (90.7%)	23 (95.8%)	
QRS Duration	≤120 ms	161 (78.9%)	16 (66.7%)	0.173
	>120 ms	43 (21.1%)	8 (33.3%)	
NYHA Class	I	0 (0%)	1 (4.2%)	**<0.001**
	II	69 (33.8%)	18 (75%)	
	III	125 (61.3%)	5 (20.8%)	
	IV	10 (4.9%)	0 (0%)	
Creatinine	<2 mg/dL	176 (86.3%)	20 (83.3%)	0.695
	>2 mg/dL	28 (13.7%)	4 (16.7%)	
	Mean ± SD	1.47 ± 0.79	1.44 ± 0.55	0.803
Ejection Fraction	Mean ± SD	29.70 ± 5.79	29.45 ± 5.14	0.845

Table 8

AF = atrial fibrillation; ICMP = ischaemic cardiomyopathy; NICMP = non-ischaemic cardiomyopathy; NSR = normal sinus rhythm; NYHA = New York Heart Association

Context from Landmark Trials

Several pivotal trials demonstrated mortality benefit with individual agents without reporting combined target dose achievement. PARADIGM-HF[25] showed that LCZ696 reduced mortality vs. enalapril (13.3% vs. 16.5%) in patients of whom 93.1% were on a stable beta blocker dose, though the degree of target dose achievement was not specified. COPERNICUS[26] demonstrated a 35% reduction in mortality with carvedilol added to standard therapy including RAAS inhibitors. HEAAL[27] showed that high-dose losartan (150 mg) reduced the composite of death or HF admission versus low-dose (50 mg), without reporting concurrent Beta Blocker dose achievement. The absence of combined dose data in all these trials represents a methodological gap that limits real-world application. Additionally, since ICD candidacy per MADIT-2 criteria[28] requires optimization of medical therapy first, our finding that most patients remain on sub-target combined GDMT has direct implications for device referral timing.

LIMITATIONS

This study has important limitations: single-centre retrospective design, small non-consecutive sample, short 12-month follow-up, under-representation of NYHA Class I and IV patients, and insufficient numbers in Group C for statistical

analysis. Heart rate was not recorded at follow-up, precluding evaluation of the target HR question. Large prospective multicentre trials are needed to evaluate combined beta blocker and RAAS inhibitor target dose strategies and their long-term impact on outcomes.

CONCLUSION

Stratifying patients with systolic heart failure according to percentage target doses of beta blockers and RAAS inhibitor therapy facilitates systematic uptitration and improves achievement of guideline-directed medical therapy. With structured follow-up, most patients can be titrated to 15–50% of the target dose, nearly one-quarter achieve >50% of either beta blocker or ACE-I/ARB/ARNI, and only a small minority reach >50% of both drug classes. Dose optimization is largely achievable within the first three months, with further incremental gains during continued follow-up. Importantly, achieving beta blocker doses of 50–100% of the target was associated with reduced mortality irrespective of RAAS inhibitor dose, underscoring the critical role of adequate beta blockade and its implications for timing advanced therapies such as ICD or CRT after optimal medical management.

REFERENCES

1. Callender T, Woodward M, Roth G, et al. Heart failure care in low-and middle-income countries: a systematic review and meta-analysis. PLoS Medicine 2014;11(8):e1001699.
2. Figueroa MS. Peters JI. Congestive Heart Failure: Diagnosis, Pathophysiology, Therapy, and Implications for Respiratory Care. Respiratory Care 2006;51(4):403-12.
3. Ohtani T, Mohammed SF, Yamamoto K. Diastolic stiffness as assessed by diastolic wall strain is associated with adverse remodeling and poor outcomes in heart failure with preserved ejection fraction. Eur. Heart J 2012;33:1742-9.
4. Inamdar AA. Heart Failure: Diagnosis, Management and Utilization. J Clin Med 2016;5(7):62.
5. Dassanayaka S, Jones SP. Recent developments in heart failure. Circulation Research 2015;117(7):e58-63.
6. Chen J, Normand SL, Wang Y, et al. National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries, 1998-2008. JAMA 2011;306(15):1669-78.
7. DeVore AD, Hammill BG, Sharma PP, et al. In-hospital worsening heart failure and associations with mortality, readmission, and healthcare utilization. Journal of the American Heart Association 2014;3(4).
8. Wright P. Pathophysiology and management of heart failure. Clinical Pharmacist 2018.
9. Marti CN, Georgiopoulou VV, Kalogeropoulos AP. Acute heart failure: patient characteristics and pathophysiology. Curr Heart Fail Rep 2013;10(4):427-33.
10. Watson RD, Gibbs CR, Lip GY. ABC of heart failure. Clinical features and complications. BMJ 2000;320(7229):236-9.
11. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor block ervalsartan in chronic heart failure. The New England Journal of Medicine2001;345(23):1667-75.
12. Joseph J, Stephy PS, James J, et al. Guideline-directed medical therapy in heart failure patients: impact of focused care provided by a heart failure clinic in comparison to general cardiology out-patient department. Egypt Heart J 2020;72(1):53.
13. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A Randomised Trial. The Lancet 1999;353(9146):9–13.
14. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. New England Journal of Medicine 1996;334(21):1349-55.
15. Effect of Metoprolol CR/XL in Chronic Heart Failure: Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure (MERIT-HF).Lancet 1999;353(9169):2001-7.
16. Fonarow GC, Abraham WT, Albert NM, et al. Organized program to initiate lifesaving treatment in hospitalized patients with heart failure (OPTIMIZE-HF): rationale and design. American Heart Journal 2004;148(1):43-51.
17. Franciosa JA, Abraham WT, Fowler M, et al. Rationale, design, and methods for a Coreg (carvedilol) Heart Failure Registry (COHERE). Journal of Cardiac Failure 2000;6(3):264-71.
18. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. The Lancet 2010;376(9744):875-85.
19. Düngen HD, Apostolović S, Inkrot S, et al. Titration to target dose of bisoprolol vs. carvedilol in elderly patients with heart failure: the CIBIS-ELD trial. European Journal of Heart Failure 2011;13(6):670-80.
20. Greene SJ, Butler J, Albert NM, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF registry. Journal of the American College of Cardiology 2018;72(4):351-66.
21. Yamakawa H, Takeuchi M, Takaoka H, et al. Negative chronotropic effect of beta-blockade therapy reduces myocardial oxygen expenditure for non-mechanical work. Circulation 1996;94(3):340-5.
22. Thackray SD, Ghosh JM, Wright GA, et al. The effect of altering heart rate on ventricular function in patients with heart failure treated with beta-blockers. Am Heart J 2006;152(4):713.e9-13.
23. Kotecha D, Flather MD, Altman DG, et al. Heart rate and rhythm and the benefit of beta- blockers in

patients with heart failure .J Am Coll Cardiol 2017;69:2885-96.
24. Eriksen-Volnes T, Westheim A, Gullestad L, et al. β-blocker doses and heart rate in patients with heart failure: results from the national norwegian heart failure registry. Biomedicine Hub 2020;5(1):1-0.
25. McMurray JJ, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. New England Journal of Medicine 2014;371(11):993-1004.
26. Wollert KC, Drexler H. Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Trial: carvedilol as the sun and center of the β-blocker world? Circulation 2002;106(17):2164-6.
27. Konstam MA, Neaton JD, Dickstein K, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. The Lancet 2009;374(9704):1840-8.
28. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. New England Journal of Medicine 2002;346(12):877-83.