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Non-withdrawal of beta-blockers in acute decompensated chronic and de-novo heart failure: Findings from the Gulf aCute heArt failure (GULF-CARE) registry.

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Abstract

Objectives: Beta-blockers reduce mortality in heart failure (HF). However, it is not clear whether they should be temporarily withdrawn during acute heart failure (AHF).

Design: Analysis of prospectively collected data

Setting: The Gulf CARE (Gulf aCute heArt failuRe rEgistry) is a prospective multicenter study of patients hospitalized with acute heart failure in 7 Middle Eastern countries.

Participants: 5005 patients with AHF.

Outcome measures: We studied the effect of beta-blockers withdrawal on intra-hospital, 3-month and 12-month mortality and hospitalization for HF in patients with acute decompensated chronic heart failure (ADCHF) and acute de-novo heart failure (ADNHF), and a LVEF < 40%.

Results: Intra-hospital mortality was lower in patients whose beta-blocker therapy was not withdrawn in both the ADCHF and ADNHF groups. This protective effect persisted after multivariate analysis (OR 0.05, 95% CI [0.02-0.11]; OR 0.04, 95% CI [0.01-0.16]; respectively, p<0.001 for both) and propensity score matching (OR 0.08, 95% CI [0.01-0.46]; OR 0.04, 95% CI [0.01-0.16]; respectively, p<0.006 for both). At 3 months, mortality was still lower only in ADCHF patients in whom beta-blockers were maintained during initial hospitalization. However, the benefit was lost after correcting for confounding factors. Interestingly, hospitalization for HF and length of hospital stay were unaffected by beta-blockers discontinuation in all patients.

Conclusion: In summary, non-withdrawal of beta-blockers in ADCHF and ADNHF is associated with lower short-term mortality.

Trial registration number: NCT01467973.

Keywords

Heart failure, Beta-blockers, Acute decompensated chronic heart failure, Acute de-novo heart failure.

Strengths and limitations of this study

This is the first study to assess non-withdrawal of beta-blockers in de-novo heart failure.

Like any observational study, selection bias could exist. Moreover, the decision of beta-blockers withdrawal during acute heart failure could have been to different factors that we didn't account for in our analysis.

Furthermore, no information was available regarding the dose of beta-blockers; in particular whether the dose was reduced in patients who continued to have beta-blockers during acute decompensation.

Introduction

Since the publication of the MERIT-HF and CIBIS-II trials[1 2], in which beta-blockers improved survival in chronic heart failure (CHF), international guidelines recommended using this drug class as first-line treatment in CHF along with the renin-angiotensin system blockers [3]. Initial safety concerns regarding the use of beta-blockers in patients with CHF were dropped with the emergence of several studies that demonstrated up to 30% decrease in mortality and other clinical endpoints in those patients[4]. Despite the improvement in the treatment and prognosis of CHF, acute heart failure (AHF) remains a challenging condition, treatment of which is essentially symptomatic. In the EuroHeart Failure Survey II, in-hospital mortality of patients with AHF was about 7%[5], and one-year mortality above 20%[6]. The continuation of beta-blockers during AHF remains controversial and subject to clinical judgment. The Beta-blocker CONtinuation Vs. INterruption in patients with Congestive heart failure hospitalizED for a decompensation episode (B-CONVINCED) trial, a randomized, controlled, open-labeled study that compared continuation *versus* withdrawal of beta-blockers during an AHF event did not report any short-term or long-term benefit in patients assigned to continue their treatment[7]. In a post-hoc analysis of the Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) study that had a similar design to B-CONVINCED, 1-month and 3-month mortality were decreased in patients whose beta-blockers was not withdrawn during initial hospitalization[8]. However, the protective effect was lost after correcting for classical heart failure covariates.

Currently, there is no large-scale data from the Middle East with regard to beta-blockers use in heart failure. The aim of this paper is to report on use of beta-blockers in patients admitted with acute heart failure and to assess short-term and long-term consequences of withdrawal or continuation of beta-blockers in heart failure patients with left ventricular dysfunction in the Middle East.

Methods

The Gulf CARE (Gulf aCute heArt failuRe registry) is a multinational multicenter prospective observational acute heart failure survey based on cases admitted to various hospitals in 7 countries from the Gulf Middle East, namely Oman, Saudi Arabia, United Arab Emirates (UAE), Qatar, Bahrain, Yemen, and Kuwait. Details of the recruitment of patients, the study design and methods have been published previously [9 10]. In brief, we collected data, as per the case report form, of patients with acute heart failure from both genders who were above 18 years of age admitted to the participating hospitals. Recruitment started in February 2012 and ended on November 13, 2012. This was preceded by a pilot phase of 1 month in November 2011. The registry continued to follow-up patients at 3 months and 1 year. The registry protocol was approved by each participating center's institutional review board and the study was registered at clinicaltrials.gov with number NCT01467973. A written informed consent was obtained from all patients

AHF was further classified as either acute decompensated chronic heart failure (ADCHF) or acute de-novo heart failure (ADNHF). ADCHF was defined as worsening of HF in patients with a previous diagnosis or hospitalization for heart failure. ADNHF was defined as AHF in patients with no prior history of heart failure. All patients were followed-up at 3 months by telephone, and at 1 year either by telephone or by a clinic visit. The registry data was collected on-line using a dedicated Web-site including demographics, risk factors, medical history, clinical manifestations, investigations, medications with dose and management. The participating hospitals ranged from secondary care hospitals to tertiary care hospitals with interventional facilities including device therapy.

The inclusion criteria for this analysis was those patients who were on beta-blockers at admission and had a left ventricular ejection fraction (LVEF) < 40%. Those patients with preserved left ventricular function and not on beta-blockers at admission were excluded from further analysis. Furthermore, 2 cohorts were created: The first cohort—those with ADCHF and the second cohort—those with ADNHF. The main outcome measures were mortality, hospitalization for HF, and length of hospital stay.

Baseline categorical variables and outcome measures were summarized using frequency distributions whiles means and standard deviations were used for numeric variables. Outcome measures and baseline patients' characteristics were compared between the two groups: withdrawal and non-withdrawal of beta-blockers using the Chi-squared test (or Fisher's exact test when expected cell counts fell below 5) for categorical variables and the student's t test or Wilcoxon rank sum test for numeric variables. Multivariate logistic regression analysis performed for in-hospital and 3-months included variables that were significantly difference between the two groups in addition to age and gender. Adjusted Odds Ratios (OR) and 95% Confidence intervals with p values are presented in tables. All analyses were done separately for the ADCHF and ADNHF patients. In addition, several sensitivity analyses were performed. Propensity scores were computed using logistic regression with membership in the two groups as the outcome and baseline variables that were significantly different between the groups as the independent variables. These scores were used to adjusted the association between the mortality outcomes and the main variable (membership in each group) using multivariate logistic regression. Moreover, propensity score matching using the most influential variable (Inotrops) was used and the main comparison between the two groups was assessed with and without adjustment to variables that were still significantly different between the two groups even after matching. This latter analysis was not done for the ADNHF groups as the sample sizes became small after matching. Statistical significance was set at the 5% level. All analyses were done using IBM-SPSS version 23.0.

Results:

Out of the total 5005 participants in the GULF-CARE, 2208 (44.1%) patients were already on beta-blockers on inclusion. Among those, 1278 patients (57.8%) had a LVEF <40%. Further, 1018(79.9%) were diagnosed with acute decompensated chronic HF (ADCHF) and 260 (20.4%) with acute do-novo heart failure (ADNHF). As shown in table 1, Patients with ADCHF tended to have more comorbidities than patients with ADNHF. They had a higher prevalence of coronary artery disease

(CAD), chronic kidney disease (CKD), valvular heart disease, atrial fibrillation (AF) and a lower LVEF; which could explain the more common use of angiotensin receptor antagonists (ARBs), aldosterone antagonists, vitamin K antagonists (VKA) and diuretics in these patients. Interestingly, they smoked less, a phenomenon that could be due to the effect of earlier life-style changes and anti-smoking campaigns in patients with CHF.

Beta-blockers were withdrawn in 10% of the patients in the ADCHF group and 13.8% in the ADNHF group. Those ADCHF patients in whom beta-blockers were discontinued had a lower blood pressure at inclusion and half of them required inotropic support during hospitalization **(supplementary table 1).** ADNHF patients who continued beta-blockade therapy were more commonly prescribed ACE-inhibitors and required less inotropic support **(supplementary table 2).**

In the ADCHF group, 15(1.6%) in-hospital deaths occurred in patients whose beta-blocker therapy was not withdrawn as compared to 37(40.2%) when beta-blocker was discontinued (p<0.001) (**Table 2**). Multivariate analysis showed that age, gender, non-compliance to medication, SBP, DBP, creatinin and statins were not predictors of in-hospital mortality in case of non-withdrawal of beta-blockers. As expected, inotropic use was significantly associated with higher mortality in our model **(Table 3).** Nevertheless, non-withdrawal of beta-blockers was associated with less mortality risk even after correcting for all the parameters age and other parameters (OR=0.05, 95% CI: 0.022-0.112, p<0.001). To confirm our findings, we performed a propensity score matching on inotropic use **(supplementary table 3).** Non-withdrawal of Beta-blockers was associated with less mortality in the propensity model (OR=0.05, 95% CI: 0.015-0.170, p<0.001), even after correcting for variables that remained significantly different in the new model (OR=0.084, 95% CI: 0.015-0.468, p=0.005). At 3 months, fewer deaths also occurred in the group of patients whose beta-blockers therapy was not withdrawn (p= 0.038). However, after multivariate logistic regression analysis, the protection conferred by beta-blockade continuation was lost (OR=0.513, 95% CI: 0.231-1.143, p=0.10)

In the ADNHF group, 5(2.2%) in-hospital deaths occurred in patients whose beta-blocker therapy was not withdrawn as compared to 17(47.2%) when beta-blocker was discontinued (p<.001). However, mortality rates were comparable at 3 months and one year **(Table 4).** Multivariate analysis didn't show that age, gender or Ace-inhibitors- which were different among both groups- predicted mortality **(Table 5).** Similarly, to the ADCHF, inotropic use was highly associated with mortality. We also performed a propensity score matching on inotropic use **(supplementary table 4)** and confirmed that beta-blockers continuation in ADNHF has a favorable outcome (OR=0.05, 95% CI: 0.015-0.170, p<0.001), even after correcting for variables that remained significantly different along both groups in the new model (OR=0.047, 95% CI: 0.013-0.169, p<0.001). Similarly to patients with ADCHF, hospitalization for heart failure and length of stay were unaffected by the withdrawal of beta-blockers.

Discussion

This observational study demonstrates that pursuing beta-blocker therapy during acute heart failure confers to patients with chronic and de-novo heart failure cardiovascular protection and decreases mortality. Interestingly, randomized placebo-controlled trials that assessed pursuing beta-blockers versus withdrawal during AHF are missing; available data are extrapolated from post-hoc analysis. The B-convinced was designed as a non-inferiority trial and demonstrated only safety of beta-blockers during acute decompensation[7]. In a retrospective analysis of the SURVIVE study that initially assessed 2 inotropic treatments in critical patients with acute HF, the benefit associated with non-withdrawal of beta-blockers was lost after correcting for heart failure covariates; only patients who never received beta-blockers had a worse outcome as compared to patients who were on these drugs at inclusion and on discharge[8]. In a sub-analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization (ESCAPE) that assessed pulmonary artery catheter use among patients admitted with acute HF, patients already prescribed beta-blockers on admission of acute heart failure had a lower 6-month mortality risk and a shorter hospitalization stay[11]. Outcomes of the

Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF), designed as a randomized placebo-controlled trial, failed to test the superiority of milnirone to placebo in patients with ADCHF[12]. Further observational analysis showed that withdrawal of beta-blockers was associated with a greater risk of 2-month mortality and re-hospitalization for HF despite limitations due to the use of milnirone in those patients and the small number of patients analyzed[13].

Our results are comparable to previous observational studies from North America and Europe. In the Italian Survey on Acute Heart Failure, withdrawal of beta-blockers during acute HF was associated with almost 4-fold increase in the risk of intra-hospital mortality[14]. The OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) is one of the largest Northern American registries of patients admitted for acute HF. Maintenance of beta-blockers during acute decompensation was associated with better outcome in post-discharge mortality[15]. Consistent with our findings, in a recent meta-analysis that included over 2700 patients treated with beta-blockers and hospitalized for AHF, withdrawal of beta-blockers significantly increased in-hospital and short term mortality, and re-hospitalization for heart failure[16].

It is not known why withdrawal of beta-blockers in acute decompensated heart failure is associated with a worse prognosis. Activation of the sympathetic system, increase of catecholamine levels and alterations in cardiac β-receptors are the hallmark of chronic heart failure; therefore beta-blocker therapy in CHF could limit the deleterious effect of chronic β-receptor stimulation such as arrhythmias, hypertrophy and cardiomyocytes apoptosis[17]. It may be possible that withdrawal of beta-blockers in the acute phase takes away earlier protective effect of beta-adrenergic inhibition at a time when the neuro-hormonal system is activated and catecholamines are significantly increased[18].

Managing beta-blockers during acute heart failure is still unclear to most physicians. The European Society of Cardiology (ESC)[19] and the American college of Cardiology foundation (ACCF)/American heart association (AHA) [20] latest guidelines recommend initiating a beta-blocker therapy following AHF

as soon as the patient is stable and before discharge. However, uncertainty persists in regards to continuing beta-blockers during an acute decompensation.

It is not known why mortality risk reduction extends up to 3 months in ADCHF but not in ADNHF although the first group has higher cardiovascular comorbidities and more severe risk factors. One explanation could be the higher prescription of cardioprotective drugs such as ACE inhibitors, ARBs, diuretics; all having shown to reduce mortality in patients with CHF and improve the outcome [21-23]. One other explanation would also be the frequent use of beta-blockers approved for heart failure in patients with ADCHF whereas the prescription of non-HF selective beta-blockers such as atenolol was more common in ADNHF. Finally, we cannot rule out that the relatively small number of patients with ADNHF, coupled to an even smaller death rate at 3 months, does not enable us draw any meaningful conclusions on long-term mortality in those patients.

Our study has few limitations. Like any observational study, selection bias could exist. The decision of beta-blockers withdrawal during acute heart could have been to different factors that we didn't account for in our analysis. For example, beta-blocker therapy could have been stopped in the more severe patients with a poor prognosis. In addition, we couldn't determine whether the dosage of beta-blockers on admission, or any reduction during hospitalization, might have influenced the outcome. Finally, the duration of beta-blocker treatment prior to the acute heart failure event was not recorded; this variable could also be a covariate since long-term beta-blocker treatment could have been more beneficial than short-term.

Conclusion

Our study suggests non-withdrawal of beta-blocker therapy during acute decompensated heart failure reduces short-term mortality risk in patients with acute decompensated chronic and de-novo heart failure; findings that could only validated in randomized controlled trials.

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Footnotes

Contribution: KS, KFA, NA, AA-A, MA-J, BB, WA, MR, NB, HA, AA-M, HAF, AE, PP and JAS were involved in the design of the Gulf CARE registry and patient enrolment and ensuring quality control of the study. CAK designed the analysis and wrote the manuscript. ZM and RS carried out the statistical analyses. All authors approved the final version of the manuscript.

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Competing interests: None.

Table 1: Baseline characteristics of patients on beta-blockers on admission and a left ventricular ejection fraction <40% included in the Gulf-Care.

	All patients in Gulf Care **N=5005**	**Patients with ADCHF and beta-blockers, and a LVEF <40%** **N=1018**	**Patients with ADNHF and beta-blockers, and a LVEF<40%** **N=260**	**p value ***
Age (years)	59±15	61.0±13.9	59.8±13.8	0.21
Male gender	3131(62.6%)	751(73.8%)	177(68.1%)	0.07
BMI (kg/m^2)	28±6	27.7±5.8	28.1±5.7	0.26
Hypertension	3059(61.1%)	673(66.1%)	181(69.6%)	0.29
Diabetes Mellitus	2492(49.8%)	569(55.9%)	147(56.5%)	0.86
Hyperlipidemia	1799(35.9%)	464(45.6%)	106(40.8%)	0.16
Smoking	1103(22%)	162(15.9%)	67 (25.8%)	0.001
Race				
Arabs	4516(90.2%)	937 (92.0%)	232(89.2%)	0.04
Asians	473(9.5%)	77(7.6%)	28(10.8%)	
Others	16(0.3%)	4(0.4%)	-	
Past – medical history				
Known CAD	2337(46.7%)	676(66.4%)	150(57.7%)	0.008
Stroke /TIAs	404(8%)	96(9.4%)	29(11.2%)	0.40
Valvular heart disease	675(13.5%)	154(15.1%)	19(7.3%)	0.001
Atrial fibrillation	607(12%)	170(16.7%)	23(8.8 %)	0.001
CKD	744(14.9%)	215(21.1%)	28(10.8%)	0.001
Etiology				
Non-Compliance Medication	964(19%)	300(29.5%)	40(15.4%)	0.05
IHD	1365(27%)	204(20,0%)	117(45.0%)	0.67
HTN	410(8.2%)	46(4.5%)	12(4.6%)	0.26
Arrhythmia	301(6%)	61(6.0%)	11(4.2%)	0.49
Anemia	143(3.1%)	23(2.3%)	5(1.9%)	0.50

Renal failure	221(4.4%)	58(5.7%)	9(3.5%)	0.19
Clinical and biochemical parameters				
HR, b.p.m	77.6±12.8	94.4±22.4	94.6±22.3	0.92
SBP, mmHg	118±18	126.6±30.6	133.6±32.4	0.002
DBP, mmHg	70±12	76.4±17.9	80.5±19.3	0.001
LVEF (%)	36.9±14	26.6±7.1	28.8±7.2	0.001
BNP, pg/mL	5324±4523	6847±9679	5227±4924	0.21
Creatinin, mmol/L	130±116	137.7±116.3	128.5±121.9	0.24
Medications				
Carvedilol	1099(21.9%)	649(63.8%)	100 (38.5%)	0.001
Bisoprolol	626 (12.5%)	286 (28.1%)	90 (34.6%)	0.04
Metoprolol	299 (5.9%)	64 (6.3%)	35 (13.5%)	0.001
Atenolol	184 (3.6%)	19 (1.9%)	35 (13.5%)	0.001
ACE-inhibitors	2762(55.2%)	652(64.0%)	166(63.8%)	0.96
ARBs	645(12.9%)	180(17.7%)	23(8.8%)	0.001
Statins	2555(51%)	751 (73.8%)	180(69.2%)	0.14
Aspirin	3089(61.7%)	832 (81.7%)	204(78.5%)	0.23
VKA	618(12%)	221(21.7%)	19(7.3%)	0.001
Ibravadine	115(2.3%)	48(4.7%)	7(2.7%)	0.15
Aldosterone antagonists	840(16.8%)	419(41.2%)	45(17.3%)	0.001
Clopidogrel	966(19%)	301(29.6%)	81(31.2%)	0.61
Diuretics	2882(57.6%)	920(90.4%)	113(43.5%)	0.001
Inotrops use during hospitalization	783 (16%)	156 (15.3%)	51 (19.6%)	0.96

All values are given as n (%) or mean ±SD. * p value: patients with acute decompensated chronic heart failure and LVEF <40% on beta-blockers on admission vs. de – Novo heart failure and LVEF <40% on beta-blockers on admission. ADCHF = Acute decompensated chronic heart failure, ADNHF = Acute de-novo heart failure, BMI=body mass index, CAD= coronary artery disease, TIAs=transient ischemic attacks, CKD=chronic kidney disease, HR=heart rate, SBP= systolic blood pressure, DBP= diastolic blood pressure, LVEF = Left ventricular ejection fraction, VKA= Vitamin K antagonists, ARBs= Angiotensin receptor blockers.

Table 2: Effect of non-withdrawal of beta-blockers in acute decompensated chronic heart failure with beta-blocker therapy on admission and a LVEF <40%

	All patients with acute decompensated heart failure, LVEF <40% and on beta-treatment on admission **N=1018**	**Patients with acute decompensated heart failure and beta-blockers (not withdrawn during the acute stage)** **N=926(91%)**	**Patients with acute decompensated heart failure (previous beta-blockers intake and stopped during the active phase)** **N=92(9.0%)**	**p- value**
In–hospital outcome				
Death	52/1018(5.1%)	15/926(1.6%)	37/92(40.2%)	<0.001*
Length of stay	9.9±15.0	9.7±15.1	12.3±13.6	0.1
3 months follow-up				
Death	86/946(9.1%)	77/896(8.6%)	9/50(18.0%)	0.038
Hospitalization for HF	219/859(25.5%)	204/818(24.9%)	15/41(36.6%)	0.09
Length of stay (days)	8.1±7.6	8.1±7.8	7.7±4.3	0.86
At 1 year follow-up				
Death	139/880(15.8%)	128/835(15.3%)	11/45(24.4%)	0.10
Hospitalization for HF	333/741 (44.9%)	316/707 (44.7%)	17/34 (50.0%)	0.54
Length of stay (days)	9.6±12.0	9.6±12.1	10.9±11.1	0.73

The frequencies and percentages for death, hospitalization for heart failure (HF) and length of stay during hospitalization. Death rates were cumulative. All values are given as n (%) or mean ±SD.

Table 3: Multivariate analysis for intra-hospital and 3-month mortality in patients with ACDHF, a LVEF <40% and beta-blockers on admission.

	Variable	OR	95% .C.I	P value
In-hospital mortality	Age	1.022	0.991-1.055	0.17
	Gender	1.058	0.428-2.618	0.90
	Non-compliance to medication	1.736	0.642-4.698	0.27
	SBP	0.990	0.968-1.014	0.41
	DBP	1.003	0.964-1.044	0.87
	LVEF	1.053	0.998-1.003	0.07
	Creatinine	1.001	0.998-1.001	0.59
	Aspirin	1.357	0.477-3.865	0.56
	Statins	2.083	0.763-5.684	0.15
	Inotrops	20.368	8.241-50.337	<0.001*
	Beta-blockers	0.050	0.022-0.112	<0.001*
	Age	1.022	0.991-1.055	0.17
3-month mortality	Age	1.029	1.010-1.048	0.002*
	Gender	0.974	0.579-1.638	0.92
	Non-compliance to medication	1.267	0.753-2.133	0.37
	SBP	0.993	0.980-1.005	0.26
	DBP	1.005	0.984-1.026	0.66
	LVEF	1.003	0.970-1.037	0.87
	Creatinine	1.001	1.000-1.003	0.15
	Aspirin	1.516	0.828-2.777	0.17
	Statins	1.307	0.747-2.284	0.34
	Inotrops	1.456	0.759-2.793	0.25
	Beta-blockers	0.513	0.231-1.143	0.10
	Age	1.029	1.010-1.048	0.002*

SBP= systolic blood pressure, DBP = diastolic blood pressure, LVEF = Left ventricular ejection fraction.

Table 4: Effect of non-withdrawal of beta-blockers in acute decompensated de-novo heart failure with beta-blocker therapy on admission and LVEF <40%

	All patients with de-novo heart failure, LVEF <40% and on beta-blockers treatment on admission. **N=260**	**Patients with de-novo heart failure and beta-blockers (not withdrawn during the acute stage)** **N=224(86.2%)**	**Patients with de-novo heart failure (previous beta-blockers intake and stopped during the acute phase)** **N=36(13.8%)**	**p- value**
In–hospital outcome				
Death	22/260(8.5%)	5/224(2.2%)	17/36(47.2%)	<0.001*
Length of stay	9.7±16.1	9.6±16.6	10.1±12.1	0.86
3 months follow-up				
Death	9/232(3.9%)	7/214(3.3%)	2/18(11.1%)	0.14
Hospitalization for HF	39/223(17.5%)	38/207(18.4%)	1/16(6.3%)	0.31
Length of stay	8.8±9.8	8.8±9.9	8.0±NE	NE
At 1 year follow-up				
Death	15/221(6.8%)	13/206(6.3%)	2/15(13.3%)	0.27
Hospitalization for HF	61/206(29.6%)	73/193(37.8%)	3/13(23.1%)	0.38
Length of stay	7.9±7.5	8.2±7.6	2.7±2.1	0.21

The frequencies and percentages for death, hospitalization for heart failure (HF) and length of stay during hospitalization. Death rates were cumulative. All values are given as n(%) or mean ±SD.

Table 5: Multivariate analysis for intra-hospital death in patients with ADNHF, a LVEF <40% and beta-blockers on admission

Variable	OR	95 % C.I	P value
Age	1.047	0.992-1.105	0.097
Gender	2.179	0.431-10.989	0.346
ACE-inhibitors	1.112	0.215-5.757	0.899
Inotrops	172.272	16.002-1854.600	<0.001*
Beta-blockers	0.018	0.003-0.122	<0.001*

SBP= systolic blood pressure, DBP = diastolic blood pressure, LVEF = Left ventricular ejection fraction.

Supplementary table 1: Baseline characteristics of patients with ADCHF and a left ventricular ejection fraction <40%, on Beta-Blockers included in the Gulf-Care.

	Patients with ADCHF with a LVEF <40% and Beta- Blockers on admission **N=1018**	**Beta-Blockers at discharge.** **N=926**	**No Beta-Blockers at discharge.** **N=92**	**p value**
Age (years)	61.0±13.9	61.1±13.7	60.3±15.8	0.64
Male gender	751(73.8%)	689(74.4%)	62(67.4%)	0.14
BMI (kg/m^2)	27.7±5.8	27.6±5.8	28.3±5.7	0.28
Hypertension	673(66.1%)	620(67.0%)	53(57.6%)	0.07
Diabetes Mellitus	569(55.9%)	518(55.9%)	51(55.4%)	0.92
Hyperlipidemia	464(45.6%)	419(45.2%)	45(48.9%)	0.50
Smoking	162(15.9%)	149(16.1%)	13(14.1%)	0.62
Race				
Arabs	937 (92.0%)	852(92.0%)	85(92.4%)	0.37
Asians	77(7.6%)	71(7.7%)	6(6.5%)	
Others	4(0.4%)	3(0.3%)	1(1.1%)	
Past – medical history				
Known CAD	676(66.4%)	617(66.6%)	59(64.1%)	0.62
Stroke /TIAs	96(9.4%)	89(9.6%)	7(7.6%)	0.53
Valvular heart disease	154(15.1%)	139(15.0%)	15(16.3%)	0.74
Atrial fibrillation	170(16.7%)	157(17.0%)	13(14.1%)	0.48
CKD	215(21.1%)	192(20.7%)	23(25.0%)	0.33
Etiology				
Non-Compliance Medication	300(29.5%)	281(30.3%)	19(20.7%)	0.052
IHD	204(20,0%)	184(19.9%)	20(21.7%)	0.66
HTN	46(4.5%)	44(4.8%)	2(2.2%)	0.42
Arrhythmia	61(6.0%)	57(6.2%)	4(4.3%)	0.48
Anemia	23(2.3%)	20(2.2%)	3(3.3%)	0.45
Renal failure	58(5.7%)	50(5.4%)	8(8.7%)	0.19
Clinical and biochemical parameters				

HR, b.p.m	94.4±22.4	94.8±22.5	91.1±21.2	0.14
SBP, mmHg	126.6±30.6	127.8±30.3	114.2±31.3	<0.001
DBP, mmHg	76.4±17.9	77.2±17.8	67.8±17.2	<0.001
LVEF (%)	26.6±7.1	26.7±7.1	25.6±7.6	0.16
BNP, pg/mL	6847±9679	6851±9831	6777±7271	0.97
Creatinin, mmol/L	137.7±116.3	135.7±113.4	158.5±141.4	0.07
Medications				
Carvedilol	649(63.8%)	589 (63.6%)	60(65.2%)	0.75
Bisoprolol	286 (28.1%)	265(28.6%)	21(22.8%)	0.23
Metoprolol	64 (6.3%)	57(6.2%)	7(7.6%)	0.58
Atenolol	19 (1.9%)	15(1.6%)	4(4.3%)	0.08
ACE-inhibitors	652(64.0%)	600(64.8%)	52(56.5%)	0.11
ARBs	180(17.7%)	167 (18.0%)	13(14.1%)	0.34
Statins	751 (73.8%)	694(74.9%)	57(62.0%)	0.007
Aspirin	832 (81.7%)	768(82.9%)	64(69.6%)	0.002
VKA	221(21.7%)	196 (21.2%)	25(27.2%)	0.18
Ibravadine	48(4.7%)	42 (4.5%)	6(6.5%)	0.43
Aldosterone antagonists	419(41.2%)	383 (41.4%)	36 (39.1%)	0.67
Clopidogrel	301(29.6%)	274 (29.6%)	27(29.3%)	0.96
Diuretics	920(90.4%)	835(90.2%)	85(92.4%)	0.49
Inotrops use during hospitalization	156 (15.3%)	110 (11.9%)	46 (50.0%)	<0.001*

All values are given as n (%) or mean ±SD. ADCHF = Acute decompensatec chronic heart failure, BMI=body mass index, CAD= coronary artery disease, TIAs=transient ischemic attacks, CKD=chronic kidney disease, HR=heart rate, SBP= systolic blood pressure, DBP= diastolic blood pressure, LVEF = Left ventricular ejection fraction, VKA= Vitamin K antagonists, ARBs= Angiotensin receptor blockers.

Supplementary table 2: Baseline characteristics of patients with ADNHF and a left ventricular ejection fraction <40%, on Beta-Blockers, included in the Gulf-Care.

	Patients with ADCHF with a LVEF <40% and Beta- Blockers on admission **N=260**	**Beta-Blockers at discharge.** **N=224**	**No Beta-Blockers at discharge.** **N=36**	**p**
Age (years)	59.8±13.8	60.1±13.8	57.9±13.9	0.35
Male gender	177(68.1%)	151(67.4%)	26(72.2%)	0.56
BMI (kg/m^2)	28.1±5.7	28.1±5.8	28.1±5.2	0.99
Hypertension	181(69.6%)	158(70.5%)	23(63.9%)	0.42
Diabetes Mellitus	147(56.5%)	123(54.9%)	24(66.7%)	0.18
Hyperlipidemia	106(40.8%)	92(41.1%)	14(38.9%)	0.80
Smoking	67 (25.8%)	60(26.8%)	7(19.4%)	0.35
Race				
Arabs	232(89.2%)	201 (89.7%)	31(86.1%)	0.56
Asians	28(10.8%)	23(10.3%)	5(13.9%)	
Others	-	-	-	
Past – medical history				
Known CAD	150(57.7%)	130(58.0%)	20(55.6%)	0.78
Stroke /TIAs	29(11.2%)	24(10.7%)	5(13.9%)	0.57
Valvular heart disease	19(7.3%)	16(7.1%)	3 (8.3%)	0.73
Atrial fibrillation	23(8.8 %)	19(8.5%)	4(11.1%)	0.53
CKD	28(10.8%)	22(9.8%)	6 (16.7%)	0.24
Etiology				
Non-Compliance Medication	40(15.4%)	37(16.5%)	3(8.3%)	0.20
IHD	117(45.0%)	100(44.6%)	17(47.2%)	0.77
HTN	12(4.6%)	11(4.9%)	1(2.8%)	0.99
Arrhythmia	11(4.2%)	8(3.6%)	3(8.3%)	0.18
Anemia	5(1.9%)	5(2.2%)	0(0.0%)	0.99
Renal failure	9(3.5%)	8(3.6%)	1(2.8%)	0.99
Clinical and biochemical				

parameters				
HR, b.p.m	94.6±22.3	94.6±21.2	94.7±28.7	0.99
SBP, mmHg	133.6±32.4	134.6±31.9	126.8±35.0	0.19
DBP, mmHg	80.5±19.3	81.0±18.8	77.6±22.4	0.34
LVEF (%)	28.8±7.2	29.0±7.2	27.5±7.4	0.23
BNP, pg/mL	5227±4924	5361±5046	3883±1614	0.52
Creatinin, mmol/L	128.5±121.9	124.9±123.5	151.1±110.2	0.23
Medications				
Carvedilol	100 (38.5%)	84(37.5%)	16(44.4%)	0.42
Bisoprolol	90 (34.6%)	82(36.6%)	8(22.2%)	0.09
Metoprolol	35 (13.5%)	25 (11.2%)	10(27.8%)	0.01
Atenolol	35 (13.5%)	33 (14.7%)	2(5.6%)	0.18
ACE-inhibitors	166(63.8%)	150(67.0%)	16(44.4%)	0.009
ARBs	23(8.8%)	18(8.0%)	5(13.9%)	0.33
Statins	180(69.2%)	154(68.8%)	26(72.2%)	0.67
Aspirin	204(78.5%)	176(78.6%)	28(77.8%)	0.91
VKA	19(7.3%)	16(7.1%)	3(8.3%)	0.73
Ibravadine	7(2.7%)	7(3.1%)	0(0.0%)	0.59
Aldosterone antagonists	45(17.3%)	38(17.0%)	7(19.4%)	0.71
Clopidogrel	81(31.2%)	69(30.8%)	12(33.3%)	0.76
Diuretics	113(43.5%)	98(43.8%)	15(41.7%)	0.81
Inotrops use during hospitalization	51 (19.6%)	32 (14.3%)	19 (52.8%)	<0.001

All values are given as n (%) or mean ±SD. ADNHF = Acute de-novo heart failure, BMI=body mass index, CAD= coronary artery disease, TIAs=transient ischemic attacks, CKD=chronic kidney disease, HR=heart rate, SBP= systolic blood pressure, DBP= diastolic blood pressure, LVEF = Left ventricular ejection fraction, VKA= Vitamin K antagonists, ARBs= Angiotensin receptor blockers.

Supplementary table 3: Variables after propensity score matching on inotrops in patients with ADCHF, a LVEF <40% and on beta-blockers on admission.

	Beta-blockers at discharge N=92	**No Beta-blockers at discharge N=92**	**p value**
Age (years)	60.3±12.7	60.3±15.8	0.98
Male gender	74 (80.4%)	62(67.4%)	0.044*
Noncompliance with medication	51 (55.4%)	19 (20.7%)	<0.001*
SBP, mmHg	147.5±39.8	114.2±31.3	<0.001*
DBP, mmHg	95.9±23.4	67.8±17.2	<0.001*
LVEF (%)	28.3±6.7	25.6±7.6	0.011*
Creatinin, mmol/L	126.7±103.4	158.5±141.4	0.08
Statins	79 (85.9%)	57(62.0%)	<0.001*
Aspirin	92 (100.0%)	64(69.6%)	<0.001*
Inotrops	46 (50.0%)	46 (50.0%)	1.000

All values are given as n (%) or mean ±SD. SBP= systolic blood pressure, DBP= diastolic blood pressure, LVEF = Left ventricular ejection fraction.

Supplementary table 4: Variables after propensity score matching on inotrops in patients with ADNHF, a LVEF <40% and on beta-blockers on admission.

	Beta Blocker at discharge N=36	**No Beta Blocker at discharge n=36**	**p value**
Age	59.9±12.7	57.9±13.9	0.514
Gender	11 (30.6%)	10 (27.8%)	0.795
ACE-inhibitors	25 (69.4%)	16 (44.4%)	0.032*
Inotrops	19 (52.8%)	19 (52.8%)	1.000

All values are given as n (%) or mean ±SD. SBP= systolic blood pressure, DBP= diastolic blood pressure, LVEF = Left ventricular ejection fraction.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract- done page 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found- done page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported- done page 4
Objectives	3	State specific objectives, including any prespecified hypotheses- done page 4
Methods		
Study design	4	Present key elements of study design early in the paper- done page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection- done page 5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up- done page 5 *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls- not applicable *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants. not applicable
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed, not applicable *Case-control study*—For matched studies, give matching criteria and the number of controls per case- not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable-done page 5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group-done page 5
Bias	9	Describe any efforts to address potential sources of bias-done page 6
Study size	10	Explain how the study size was arrived at-done page 5 to 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why-done page 6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding- done page 6
		(*b*) Describe any methods used to examine subgroups and interactions-done page 6
		(*c*) Explain how missing data were addressed-done page 6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed- done page 7 *Case-control study*—If applicable, explain how matching of cases and controls was addressed not applicable *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy not applicable
		(*e*) Describe any sensitivity analyses-done page 6

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed- page 6
		(b) Give reasons for non-participation at each stage- page 6-7
		(c) Consider use of a flow diagram- not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders- done page 6-7 and table 1
		(b) Indicate number of participants with missing data for each variable of interest- done page 6-7
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)- done page 7-8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time- done table 2 and 4
		Case-control study—Report numbers in each exposure category, or summary measures of exposure-not applicable.
		Cross-sectional study—Report numbers of outcome events or summary measures-not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included- done page 6 to 8
		(*b*) Report category boundaries when continuous variables were categorized- done page 6 to 8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses- done page 7-8
Discussion		
Key results	18	Summarise key results with reference to study objectives- done page 8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias - done page 10.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence- done pages from 8 to 10
Generalisability	21	Discuss the generalisability (external validity) of the study results-done page 10
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based- done page 13.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Non-withdrawal of beta-blockers in acute decompensated chronic and de-novo heart failure in a prospective multicenter study of patients with acute heart failure in the Middle East.

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Non-withdrawal of beta-blockers in acute decompensated chronic and de-novo heart failure in a prospective multicenter study of patients with acute heart failure in the Middle East.

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Abstract

Objectives: Beta-blockers reduce mortality in heart failure (HF). However, it is not clear whether they should be temporarily withdrawn during acute HF.

Design: Analysis of prospectively collected data

Setting: The GULF-CARE (Gulf aCute heArt failuRe rEgistry) is a prospective multicenter study of patients hospitalized with acute HF in 7 Middle Eastern countries.

Participants: 5005 patients with acute HF.

Outcome measures: We studied the effect of beta-blockers non-withdrawal on intra-hospital, 3-month and 12-month mortality and hospitalization for HF in patients with acute decompensated chronic heart failure (ADCHF) and acute de-novo heart failure (ADNHF), and a LVEF < 40%.

Results: 44.1% of patients were already on beta-blockers on inclusion. Among those, 57.8% had a LVEF <40%. Further, 79.9% were diagnosed with ADCHF and 20.4% with ADNHF. Mean age was 61 (13.9) in the ADCHF group and 59.8 (13.8) in the ADNHF group. Ischemic heart disease was the precipitating factor in 20% of the ADCHF group and 45% in the ADNHF. Intra-hospital mortality was lower in patients whose beta-blocker therapy was not withdrawn in both the ADCHF and ADNHF groups. This protective effect persisted after multivariate analysis (OR 0.05, 95% CI [0.02-0.11]; OR 0.04, 95% CI [0.01-0.16]; respectively, p<0.001 for both) and propensity score matching (OR 0.08, 95% CI [0.01-0.46]; OR 0.04, 95% CI [0.01-0.16]; respectively, p<0.006 for both). At 3 months, mortality was still lower only in ADCHF patients in whom beta-blockers were maintained during initial hospitalization. However, the benefit was lost after correcting for confounding factors. Interestingly, hospitalization for HF and length of hospital stay were unaffected by beta-blockers discontinuation in all patients.

Conclusion: In summary, non-withdrawal of beta-blockers in acute decompensated chronic heart failure and acute de-novo heart failure is associated with lower intra-hospital mortality.

Trial registration number: NCT01467973.

Keywords

Heart failure

Beta-blockers

Acute decompensated chronic heart failure

Acute de-novo heart failure

Strengths and limitations of this study

This is the first study to assess non-withdrawal of beta-blockers in de-novo heart failure.

Like any observational study, selection bias could exist. Moreover, the decision of beta-blocker withdrawal during acute heart failure could have been due to different factors that we did not account for in our analysis.

Furthermore, no information was available regarding the dose of beta-blockers, in particular whether the dose was reduced in patients who continued to use beta-blockers during acute decompensation.

Introduction

Since the publication of the MERIT-HF, CIBIS-II, US Carvedilol Heart failure and COPERNICUS trials[1-4], in which beta-blockers improved survival in heart failure (HF) patients, international guidelines recommended using this drug class as first-line treatment in chronic HF along with the renin-angiotensin system blockers[5]. Initial safety concerns regarding the use of beta-blockers in patients with HF were dropped with the emergence of several studies that demonstrated up to 30% decrease in mortality risk in those patients[6]. Despite the improvement in the treatment and prognosis of chronic HF, acute HF remains a challenging condition, treatment of which is essentially symptomatic. In the EuroHeart Failure Survey II, in-hospital mortality of patients with acute HF was about 7%[7], and one-year mortality above 20%[8]. The continuation of beta-blockers during acute HF remains controversial and subject to clinical judgment. The Beta-blocker CONtinuation Vs. INterruption in patients with Congestive heart failure hospitalizED for a decompensation episode (B-CONVINCED) trial, a randomized, controlled, open-labeled study that compared continuation *versus* withdrawal of beta-blockers during acute HF did not report any short-term or long-term benefit in patients assigned to continue their treatment[9]. In a post-hoc analysis of the Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) study that had a similar design to B-CONVINCED, 1-month and 3-month mortality decreased in patients whose beta-blockers were not withdrawn during initial hospitalization[10]. However, the protective effect was lost after correcting for classical heart failure covariates.

Currently, there is no large-scale data from the Middle East (ME) with regard to beta-blockers use in HF. The aim of this paper is to report on use of beta-blockers in patients admitted with acute HF and to assess short-term and long-term consequences of withdrawal or continuation of beta-blockers in HF patients with left ventricular dysfunction in the ME.

Methods

The Gulf CARE (Gulf aCute heArt failuRe registry) is a multinational multicenter prospective observational acute heart failure survey based on cases admitted to various hospitals in 7 countries from the Gulf Middle East, namely Oman, Saudi Arabia, United Arab Emirates (UAE), Qatar, Bahrain, Yemen, and Kuwait. Details of the recruitment of patients, the study design and methods have been published previously [11 12]. In brief, we collected data, as per the case report form, of patients with acute HF from both genders who were above 18 years of age admitted to the participating hospitals. Recruitment started in February 2012 and ended on November 13, 2012. This was preceded by a pilot phase of 1 month in November 2011. The registry continued to follow-up patients at 3 months and 1 year. The registry protocol was approved by each participating center's research ethics committee or institutional review board (IRB): Directorate of research and studies, Ministry of Health - Sultanate of Oman; King Saud University's IRB, Kingdom of Saudi Arabia; Sheikh Khalifa medical city's IRB, UAE; Hamad Medical Corporation's IRB, Qatar; Mohammed Bin khalifa cardiac center's IRB, Bahrain; Sana'a University' IRB, Yemen and Ministry of health's IRB in Kuwait) .The study was registered at clinicaltrials.gov with number NCT01467973. A written informed consent was obtained from all patients

Acute HF was further classified as either acute decompensated chronic heart failure (ADCHF) or acute de-novo heart failure (ADNHF). ADCHF was defined as worsening of HF in patients with a previous diagnosis or hospitalization for HF. ADNHF was defined as acute HF in patients with no prior history of heart failure. All patients were followed-up at 3 months by telephone, and at 1 year either by telephone or by a clinic visit. The registry data was collected on-line using a dedicated Web-site including demographics, risk factors, medical history, clinical manifestations, investigations, medications with dose and management. The participating hospitals ranged from secondary care hospitals to tertiary care hospitals with interventional facilities including device therapy.

The inclusion criteria for this analysis was those patients who were on beta-blockers at time of admission and had a left ventricular ejection fraction (LVEF) < 40%. Those patients with preserved left ventricular function and not on beta-blockers at time of admission were excluded from further analysis. Furthermore, 2 cohorts were created, the first with ADCHF and the second with ADNHF. The main outcome measures were mortality, hospitalization for HF, and length of hospital stay.

Baseline categorical variables and outcome measures were summarized using frequency distributions whiles means and standard deviations were used for numeric variables. Outcome measures and baseline patients' characteristics were compared between the two groups: withdrawal and non-withdrawal of beta-blockers using the Chi-squared test (or Fisher's exact test when expected cell counts fell below 5) for categorical variables and the student's t test or Wilcoxon rank sum test for numeric variables. Multivariate logistic regression analysis performed for in-hospital and 3-months included variables that were significantly different between the two groups in addition to age and gender. Adjusted Odds Ratios (OR) and 95% Confidence intervals with p values are presented. All analyses were done separately for the ADCHF and ADNHF patients. In addition, several sensitivity analyses were performed. Propensity scores were computed using logistic regression with membership in the two groups as the outcome and baseline variables that were significantly different between the groups as the independent variables. These scores were used to adjust the association between the mortality outcomes and the main variable (membership in each group) using multivariate logistic regression. Moreover, propensity score matching using the most influential variable (inotropes) was used and the main comparison between the two groups was assessed with and without adjustment to variables that were still significantly different between the two groups even after matching. This latter analysis was not done for the ADNHF groups as the sample sizes became small after matching. Statistical significance was set at the 5% level. All analyses were done using IBM-SPSS version 23.0.

Results:

Out of the total 5005 participants in the GULF-CARE, 2208 (44.1%) patients were already on beta-blockers on inclusion. Further, beta-blockers were prescribed in 1278 (42.2%) patients with a LVEF <40%. Among those, 1018 (79.9%) were diagnosed with acute decompensated chronic HF (ADCHF) and 260 (20.4%) with acute do-novo heart failure (ADNHF). As shown in table 1, Patients with ADCHF tended to have more comorbidities than patients with ADNHF. They had a higher prevalence of coronary artery disease (CAD), chronic kidney disease (CKD), valvular heart disease, atrial fibrillation (AF) and a lower LVEF; which could explain the more common use of angiotensin receptor antagonists (ARBs), aldosterone antagonists, vitamin K antagonists (VKA) and diuretics in these patients. Interestingly, they smoked less, a phenomenon that could be due to the effect of earlier life-style changes and anti-smoking campaigns in patients with CHF.

Table 1: Baseline characteristics of patients on beta-blockers on admission and a left ventricular ejection fraction <40% included in the Gulf-Care.

	All patients in Gulf Care N=5005	**Patients with a LVEF <40% on beta-blockers on admission N=1278**		**P value ***
		Patients with ADCHF and a LVEF <40%, on beta-blockers on admission. N=1018	**Patients with ADNHF and a LVEF<40%, on beta-blockers on admission. N=260**	
Age (years)	59±15	61.0±13.9	59.8±13.8	0.21
Male gender	3131(62.6%)	751(73.8%)	177(68.1%)	0.07
BMI (kg/m^2)	28±6	27.7±5.8	28.1±5.7	0.26
Hypertension	3059(61.1%)	673(66.1%)	181(69.6%)	0.29
Diabetes Mellitus	2492(49.8%)	569(55.9%)	147(56.5%)	0.86

Hyperlipidemia	1799(35.9%)	464(45.6%)	106(40.8%)	0.16
Smoking	1103(22%)	162(15.9%)	67 (25.8%)	0.001
Race				
Arabs	4516(90.2%)	937 (92.0%)	232(89.2%)	0.04
Asians	473(9.5%)	77(7.6%)	28(10.8%)	
Others	16(0.3%)	4(0.4%)	-	
Past – medical history				
Known CAD	2337(46.7%)	676(66.4%)	150(57.7%)	0.008
Stroke /TIAs	404(8%)	96(9.4%)	29(11.2%)	0.40
Valvular heart disease	675(13.5%)	154(15.1%)	19(7.3%)	0.001
Atrial fibrillation	607(12%)	170(16.7%)	23(8.8 %)	0.001
CKD	744(14.9%)	215(21.1%)	28(10.8%)	0.001
Etiology				
Non-Compliance Medication	964(19%)	300(29.5%)	40(15.4%)	0.05
IHD	1365(27%)	204(20,0%)	117(45.0%)	0.67
HTN	410(8.2%)	46(4.5%)	12(4.6%)	0.26
Arrhythmia	301(6%)	61(6.0%)	11(4.2%)	0.49
Anemia	143(3.1%)	23(2.3%)	5(1.9%)	0.50
Renal failure	221(4.4%)	58(5.7%)	9(3.5%)	0.19
Clinical and biochemical parameters				
HR, b.p.m	77.6±12.8	94.4±22.4	94.6±22.3	0.92
SBP, mmHg	118±18	126.6±30.6	133.6±32.4	0.002
DBP, mmHg	70±12	76.4±17.9	80.5±19.3	0.001
LVEF (%)	36.9±14	26.6±7.1	28.8±7.2	0.001
BNP, pg/mL	5324±4523	6847±9679	5227±4924	0.21
Creatinine, mmol/L	130±116	137.7±116.3	128.5±121.9	0.24
Medications				

Carvedilol	1099(21.9%)	649(63.8%)	100 (38.5%)	0.001
Bisoprolol	626 (12.5%)	286 (28.1%)	90 (34.6%)	0.04
Metoprolol	299 (5.9%)	64 (6.3%)	35 (13.5%)	0.001
Atenolol	184 (3.6%)	19 (1.9%)	35 (13.5%)	0.001
ACE-inhibitors	2762(55.2%)	652(64.0%)	166(63.8%)	0.96
ARBs	645(12.9%)	180(17.7%)	23(8.8%)	0.001
Statins	2555(51%)	751 (73.8%)	180(69.2%)	0.14
Aspirin	3089(61.7%)	832 (81.7%)	204(78.5%)	0.23
VKA	618(12%)	221(21.7%)	19(7.3%)	0.001
Ibravadine	115(2.3%)	48(4.7%)	7(2.7%)	0.15
Aldosterone antagonists	840(16.8%)	419(41.2%)	45(17.3%)	0.001
Clopidogrel	966(19%)	301(29.6%)	81(31.2%)	0.61
Diuretics	2882(57.6%)	920(90.4%)	113(43.5%)	0.001
Inotropes use during hospitalization	783 (16%)	156 (15.3%)	51 (19.6%)	0.96

All values are given as n (%) or mean ±SD. * p value: patients with acute decompensated chronic heart failure and LVEF <40% on beta-blockers on admission vs. de – Novo heart failure and LVEF <40% on beta-blockers on admission. ADCHF = Acute decompensated chronic heart failure, ADNHF = Acute de-novo heart failure, BMI=body mass index, CAD= coronary artery disease, TIAs=transient ischemic attacks, CKD=chronic kidney disease, HR=heart rate, SBP= systolic blood pressure, DBP= diastolic blood pressure, LVEF = Left ventricular ejection fraction, VKA= Vitamin K antagonists, ARBs= Angiotensin receptor blockers.

Beta-blockers were withdrawn in 10% of the patients in the ADCHF group and 13.8% in the ADNHF group. Those ADCHF patients in whom beta-blockers were discontinued had a lower blood pressure at inclusion and half of them required inotropic support during hospitalization **(supplementary table 1).** ADNHF patients who continued beta-blockade therapy were more commonly prescribed ACE-inhibitors and required less inotropic support **(supplementary table 2).**

In the ADCHF group, 15 (1.6%) in-hospital deaths occurred in patients whose beta-blocker therapy was not withdrawn as compared to 37 (40.2%) when beta-blockers were discontinued (p<0.001) (**Table 2**).

Table 2: Effect of non-withdrawal of beta-blockers in acute decompensated chronic heart failure with beta-blocker therapy on admission and a LVEF <40%

	All patients with acute decompensated heart failure, LVEF <40% and on beta-treatment on admission **N=1018**	**Beta-blockers maintained during hospitalization** **N=926(91%)**	**Beta-blockers withdrawn during hospitalization** **N=92(9.0%)**	**P value**
In–hospital outcome				
Death	52/1018(5.1%)	15/926(1.6%)	37/92(40.2%)	<0.001*
Length of stay	9.9±15.0	9.7±15.1	12.3±13.6	0.1
3-month follow-up				
Death	86/946(9.1%)	77/896(8.6%)	9/50(18.0%)	0.038
Hospitalization for HF	219/859(25.5%)	204/818(24.9%)	15/41(36.6%)	0.09
Length of stay (days)	8.1±7.6	8.1±7.8	7.7±4.3	0.86
12-month follow-up				
Death	139/880(15.8%)	128/835(15.3%)	11/45(24.4%)	0.10
Hospitalization for HF	333/741 (44.9%)	316/707 (44.7%)	17/34 (50.0%)	0.54
Length of stay (days)	9.6±12.0	9.6±12.1	10.9±11.1	0.73

The frequencies and percentages for death, hospitalization for heart failure (HF) and length of stay during hospitalization. Death rates were cumulative. All values are given as n (%) or mean ±SD.

Multivariate analysis showed that age, gender, non-compliance to medication, SBP, DBP, creatinine and statins were not predictors of in-hospital mortality in case of non-withdrawal of beta-blockers. As expected, inotropic use was significantly associated with higher mortality in our model **(Table 3).**

Table 3: Multivariate analysis for intra-hospital and 3-month mortality in patients with ACDHF, a LVEF <40% and beta-blockers on admission.

	Variable	OR	95% .C.I	P value
In-hospital mortality	Age	1.022	0.991-1.055	0.17
	Gender	1.058	0.428-2.618	0.90
	Non-compliance to medication	1.736	0.642-4.698	0.27
	SBP	0.990	0.968-1.014	0.41
	DBP	1.003	0.964-1.044	0.87
	LVEF	1.053	0.998-1.003	0.07
	Creatinine	1.001	0.998-1.001	0.59
	Aspirin	1.357	0.477-3.865	0.56
	Statins	2.083	0.763-5.684	0.15
	Inotropes	20.368	8.241-50.337	<0.001*
	Beta-blockers on discharge			
	Beta-blockers withdrawn (reference group)	1	-	
	Beta-blockers maintained	0.050	0.022-0.112	<0.001*

3-month mortality	Age	1.029	1.010-1.048	0.002*
	Gender	0.974	0.579-1.638	0.92
	Non-compliance to medication	1.267	0.753-2.133	0.37
	SBP	0.993	0.980-1.005	0.26
	DBP	1.005	0.984-1.026	0.66
	LVEF	1.003	0.970-1.037	0.87
	Creatinine	1.001	1.000-1.003	0.15
	Aspirin	1.516	0.828-2.777	0.17
	Statins	1.307	0.747-2.284	0.34
	Inotropes	1.456	0.759-2.793	0.25
	Beta-blockers on discharge			
	Beta-blockers withdrawn (reference group)	1		
	Beta-blockers maintained	0.513	0.231-1.143	0.10

SBP= systolic blood pressure, DBP = diastolic blood pressure, LVEF = Left ventricular ejection fraction.

Nevertheless, non-withdrawal of beta-blockers was associated with less mortality risk even after correcting for all the parameters (OR=0.05, 95% CI: 0.022-0.112, p<0.001). To confirm our findings, we performed a propensity score matching on inotropic use **(supplementary Table 3).** Non-withdrawal of beta-blockers was associated with less mortality in the propensity model (OR=0.05, 95% CI: 0.015-0.170, p<0.001), even after correcting for variables that remained significantly different in the new model (OR=0.084, 95% CI: 0.015-0.468, p=0.005). At 3 months, fewer deaths also occurred in the group of patients whose beta-blockers therapy was not withdrawn (p= 0.038). However, after multivariate logistic regression analysis, the protection conferred by beta-blockade continuation was lost (OR=0.513, 95% CI: 0.231-1.143, p=0.10).

In the ADNHF group, 5 (2.2%) in-hospital deaths occurred in patients whose beta-blocker therapy was not withdrawn as compared to 17 (47.2%) when beta-blockers were discontinued (p<0.001). However, mortality rates were comparable at 3 months and one year **(Table 4).**

Table 4: Effect of non-withdrawal of beta-blockers in acute decompensated de-novo heart failure with beta-blocker therapy on admission and LVEF <40%

	All patients with de-novo heart failure, LVEF <40% and on beta-blockers treatment on admission. **N=260**	**Beta-blockers maintained during hospitalization** **N=224(86.2%)**	**Beta-blockers withdrawn during hospitalization** **N=36(13.8%)**	**p- value**
In–hospital outcome				
Death	22/260(8.5%)	5/224(2.2%)	17/36(47.2%)	<0.001*
Length of stay	9.7±16.1	9.6±16.6	10.1±12.1	0.86
3 months follow-up				
Death	9/232(3.9%)	7/214(3.3%)	2/18(11.1%)	0.14
Hospitalization for HF	39/223(17.5%)	38/207(18.4%)	1/16(6.3%)	0.31
Length of stay	8.8±9.8	8.8±9.9	8.0±NE	NE
At 1 year follow-up				
Death	15/221(6.8%)	13/206(6.3%)	2/15(13.3%)	0.27
Hospitalization for HF	61/206(29.6%)	73/193(37.8%)	3/13(23.1%)	0.38
Length of stay	7.9±7.5	8.2±7.6	2.7±2.1	0.21

The frequencies and percentages for death, hospitalization for heart failure (HF) and length of stay during hospitalization. Death rates were cumulative. All values are given as n(%) or mean ±SD.

Multivariate analysis did not show that age, gender or Ace-inhibitors, which were different among both groups, predicted mortality **(Table 5).**

Table 5: Multivariate analysis for intra-hospital death in patients with ADNHF, a LVEF <40% and beta-blockers on admission

Variable	OR	95 % C.I	P value
Age	1.047	0.992-1.105	0.097
Gender	2.179	0.431-10.989	0.346
ACE-inhibitors	1.112	0.215-5.757	0.899
Inotrops	172.272	16.002-1854.600	<0.001*
Beta-blockers			
Beta-blockers withdrawn (reference group)	1		
Beta-blockers maintained	0.018	0.003-0.122	<0.001*

SBP= systolic blood pressure, DBP = diastolic blood pressure, LVEF = Left ventricular ejection fraction.

Similarly, to the ADCHF, inotropic use was highly associated with mortality. We also performed a propensity score matching on inotropic use **(supplementary Table 4)** and confirmed that beta-blocker continuation in ADNHF has a favorable outcome (OR=0.05, 95% CI: 0.015-0.170, p<0.001), even after correcting for variables that remained significantly different between both groups in the new model (OR=0.047, 95% CI: 0.013-0.169, p<0.001). Similarly to patients with ADCHF, hospitalization for HF and length of stay were unaffected by the withdrawal of beta-blockers.

Discussion

This observational study demonstrates that pursuing beta-blocker therapy during acute HF confers to patients with chronic and de-novo HF cardiovascular protection and decreases mortality. Interestingly, randomized placebo-controlled trials that assessed pursuing beta-blockers versus withdrawal during acute HF are missing; available data are extrapolated from post-hoc analysis. The B-convinced was designed as a non-inferiority trial and demonstrated only safety of beta-blockers during acute decompensation[9]. In a retrospective analysis of the SURVIVE study that initially assessed 2 inotropic treatments in critical patients with acute HF, the benefit associated with non-withdrawal of beta-blockers was lost after correcting for HF covariates; only patients who never received beta-blockers had a worse outcome as compared to patients who were on these drugs at inclusion and on discharge[10]. In a sub-analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization (ESCAPE) that assessed pulmonary artery catheter use among patients admitted with acute HF, patients already prescribed beta-blockers on admission had a lower 6-month mortality risk and a shorter hospitalization stay[13]. Outcomes of the Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF), designed as a randomized placebo-controlled trial, failed to test the superiority of milnirone to placebo in patients with ADCHF[14]. Further observational analysis showed that withdrawal of beta-blockers was associated with a greater risk of 2-month mortality and re-hospitalization for HF despite limitations due to the use of milnirone in those patients and the small number of patients analyzed[15].

Our results are comparable to previous observational studies from North America and Europe. In the Italian Survey on Acute Heart Failure, withdrawal of beta-blockers during acute HF was associated with almost 4-fold increase in the risk of intra-hospital mortality[16]. The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) is one of the largest Northern American registries of patients admitted with acute HF. Maintenance of beta-blockers during

acute decompensation was associated with better outcome in post-discharge mortality[17]. Consistent with our findings, Prins et al reported in a recent meta-analysis that included over 2700 patients treated with beta-blockers and hospitalized for acute HF, that withdrawal of beta-blockers significantly increased in-hospital and short term mortality, and re-hospitalization for HF [18].

Despite firm safety data and un-doubted long-term benefit, beta-blocker therapy remains under-prescribed. In our study, only 44.1% of all patients presenting with acute HF and 44.2 % of patients with a LVEF<40% were treated with beta-blockers. The frequency of beta-blockers prescription is variable according to cohorts and ranges from 32% in the "Italian Survey on Acute Heart Failure" study [16] to 53.3% in the SURVIVE study[10] and 62% in the ESCAPE trial [13].

It is not known why withdrawal of beta-blockers in acute HF is associated with a worse prognosis. Activation of the sympathetic system, increase of catecholamine levels and alterations in cardiac β-receptors are the hallmark of chronic HF; therefore beta-blocker therapy in chronic HF could limit the deleterious effect of chronic β-receptor stimulation such as arrhythmias, hypertrophy and cardiomyocytes apoptosis[19]. It may be possible that withdrawal of beta-blockers in the acute phase takes away earlier protective effect of beta-adrenergic inhibition at a time when the neuro-hormonal system is activated and catecholamines are significantly increased[20].

Managing beta-blockers during acute HF is still unclear to most physicians. The Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial investigators were the first to report that in-hospital initiation of beta-blockers was safe compared to post-discharge[21]. The latest guidelines from both the Society of Cardiology (ESC)[22] and the American college of Cardiology foundation (ACCF)/American heart association (AHA) [23] recommend initiating a beta-blocker therapy following acute HF as soon as the patient is stable and before discharge. However, uncertainty persists in regards to continuing beta-blockers during an acute decompensation. Beta-blockade therapy discontinuation during AHF is variable. In older studies such as the OPTIME-CHF, beta-blockers were

withdrawn in over 20% of patients [15]. In our study, beta-blockers were withdrawn in 10% of patients with ADCHF and 13.8% of patients with ADNHF. Those numbers are almost similar to the Italian Survey on Acute Heart Failure in which Orso et al reported a withdrawal rate of 9% in all AHF patients with beta-blockers on admission [16] However, Bohm et al reported a lower rate (6.8%) in the retrospective analysis of the SURVIVE study[10].

It is not known why mortality risk reduction extends up to 3 months in ADCHF but not in ADNHF although the first group has higher cardiovascular comorbidities and more severe risk factors. One explanation could be the higher prescription of cardioprotective drugs such as ACE inhibitors, ARBs, diuretics; all having shown to reduce mortality in patients with chronic HF and improve the outcome [24-26]. One other explanation would also be the frequent use of beta-blockers approved for HF in patients with ADCHF whereas the prescription of non-HF selective beta-blockers such as atenolol was more common in ADNHF. Finally, we cannot rule out that the relatively small number of patients with ADNHF, coupled to an even smaller death rate at 3 months, does not enable us draw any meaningful conclusions on long-term mortality in those patients.

Our study has a few limitations. Like any observational study, selection bias could exist. The decision of beta-blocker withdrawal during acute HF could have been to different factors not accounted for in our analysis. Beta-blocker therapy could have been withdrawn in the more severe patients with a poor prognosis. Despite the correction on available cofounding factors, we could have missed other markers of disease severity that were not recorded in the cohort. In addition, we could not determine whether the dosage of beta-blockers on admission, or any reduction during hospitalization, might have influenced the outcome. Finally, the duration of beta-blocker treatment prior to acute HF was not recorded; this variable could also be a confounding factor since long-term beta-blocker treatment could have been more beneficial than short-term.

Conclusion

Our study suggests non-withdrawal of beta-blocker therapy during acute heart failure reduces short-term mortality risk in patients with acute decompensated chronic and de-novo heart failure; findings that could only be validated in randomized controlled trials designed to show the superiority of non-withdrawal of beta-blockade therapy and also determine whether beta-blocker dose should be reduced or kept unchanged compared to a withdrawal strategy.

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Footnotes

Contribution: KS, KFA, NA, AA-A, MA-J, BB, WA, MR, NB, HA, AA-M, HAF, AE, PP and JAS were involved in the design of the Gulf CARE registry and patient enrolment and ensuring quality control of the study. CAK designed the analysis and wrote the manuscript. ZM and RS carried out the statistical analyses. All authors approved the final version of the manuscript.

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Supplementary table 1: Baseline characteristics of patients with acute decompensated chronic heart failure and a left ventricular ejection fraction <40%, on beta-blockers on admission

	Patients with ADCHF with a LVEF <40% and beta-blockers on admission N=1018	**Beta-blockers maintained during hospitalization N=926**	**Beta-blockers withdrawn during hospitalization N=92**	**p value**
Age (years)	61.0±13.9	61.1±13.7	60.3±15.8	0.64
Male gender	751(73.8%)	689(74.4%)	62(67.4%)	0.14
BMI (kg/m^2)	27.7±5.8	27.6±5.8	28.3±5.7	0.28
Hypertension	673(66.1%)	620(67.0%)	53(57.6%)	0.07
Diabetes Mellitus	569(55.9%)	518(55.9%)	51(55.4%)	0.92
Hyperlipidemia	464(45.6%)	419(45.2%)	45(48.9%)	0.50
Smoking	162(15.9%)	149(16.1%)	13(14.1%)	0.62
Race				
Arabs	937 (92.0%)	852(92.0%)	85(92.4%)	0.37
Asians	77(7.6%)	71(7.7%)	6(6.5%)	
Others	4(0.4%)	3(0.3%)	1(1.1%)	
Past – medical history				
Known CAD	676(66.4%)	617(66.6%)	59(64.1%)	0.62
Stroke /TIAs	96(9.4%)	89(9.6%)	7(7.6%)	0.53
Valvular heart disease	154(15.1%)	139(15.0%)	15(16.3%)	0.74
Atrial fibrillation	170(16.7%)	157(17.0%)	13(14.1%)	0.48
CKD	215(21.1%)	192(20.7%)	23(25.0%)	0.33
Etiology				
Non-Compliance Medication	300(29.5%)	281(30.3%)	19(20.7%)	0.052
IHD	204(20,0%)	184(19.9%)	20(21.7%)	0.66
HTN	46(4.5%)	44(4.8%)	2(2.2%)	0.42
Arrhythmia	61(6.0%)	57(6.2%)	4(4.3%)	0.48
Anemia	23(2.3%)	20(2.2%)	3(3.3%)	0.45
Renal failure	58(5.7%)	50(5.4%)	8(8.7%)	0.19
Clinical and biochemical parameters				

HR, b.p.m	94.4±22.4	94.8±22.5	91.1±21.2	0.14
SBP, mmHg	126.6±30.6	127.8±30.3	114.2±31.3	<0.001
DBP, mmHg	76.4±17.9	77.2±17.8	67.8±17.2	<0.001
LVEF (%)	26.6±7.1	26.7±7.1	25.6±7.6	0.16
BNP, pg/mL	6847±9679	6851±9831	6777±7271	0.97
Creatinin, mmol/L	137.7±116.3	135.7±113.4	158.5±141.4	0.07
Medications				
Carvedilol	649(63.8%)	589 (63.6%)	60(65.2%)	0.75
Bisoprolol	286 (28.1%)	265(28.6%)	21(22.8%)	0.23
Metoprolol	64 (6.3%)	57(6.2%)	7(7.6%)	0.58
Atenolol	19 (1.9%)	15(1.6%)	4(4.3%)	0.08
ACE-inhibitors	652(64.0%)	600(64.8%)	52(56.5%)	0.11
ARBs	180(17.7%)	167 (18.0%)	13(14.1%)	0.34
Statins	751 (73.8%)	694(74.9%)	57(62.0%)	0.007
Aspirin	832 (81.7%)	768(82.9%)	64(69.6%)	0.002
VKA	221(21.7%)	196 (21.2%)	25(27.2%)	0.18
Ibravadine	48(4.7%)	42 (4.5%)	6(6.5%)	0.43
Aldosterone antagonists	419(41.2%)	383 (41.4%)	36 (39.1%)	0.67
Clopidogrel	301(29.6%)	274 (29.6%)	27(29.3%)	0.96
Diuretics	920(90.4%)	835(90.2%)	85(92.4%)	0.49
Inotrops use during hospitalization	156 (15.3%)	110 (11.9%)	46 (50.0%)	<0.001*

All values are given as n (%) or mean ±SD. ADCHF = Acute decompensated chronic heart failure, BMI=body mass index, CAD= coronary artery disease, TIAs=transient ischemic attacks, CKD=chronic kidney disease, HR=heart rate, SBP= systolic blood pressure, DBP= diastolic blood pressure, LVEF = Left ventricular ejection fraction, VKA= Vitamin K antagonists, ARBs= Angiotensin receptor blockers.

Supplementary table 2: Baseline characteristics of patients with acute de-novo heart failure and a left ventricular ejection fraction <40%, on beta-Blockers on admission.

	Patients with ADCHF with a LVEF <40% and beta-blockers on admission N=260	**Beta-blockers maintained during hospitalization N=224**	**Beta-blockers withdrawn during hospitalization N=36**	**p**
Age (years)	59.8±13.8	60.1±13.8	57.9±13.9	0.35
Male gender	177(68.1%)	151(67.4%)	26(72.2%)	0.56
BMI (kg/m^2)	28.1±5.7	28.1±5.8	28.1±5.2	0.99
Hypertension	181(69.6%)	158(70.5%)	23(63.9%)	0.42
Diabetes Mellitus	147(56.5%)	123(54.9%)	24(66.7%)	0.18
Hyperlipidemia	106(40.8%)	92(41.1%)	14(38.9%)	0.80
Smoking	67 (25.8%)	60(26.8%)	7(19.4%)	0.35
Race				
Arabs	232(89.2%)	201 (89.7%)	31(86.1%)	0.56
Asians	28(10.8%)	23(10.3%)	5(13.9%)	
Others	-	-	-	
Past – medical history				
Known CAD	150(57.7%)	130(58.0%)	20(55.6%)	0.78
Stroke /TIAs	29(11.2%)	24(10.7%)	5(13.9%)	0.57
Valvular heart disease	19(7.3%)	16(7.1%)	3 (8.3%)	0.73
Atrial fibrillation	23(8.8 %)	19(8.5%)	4(11.1%)	0.53
CKD	28(10.8%)	22(9.8%)	6 (16.7%)	0.24
Etiology				
Non-Compliance Medication	40(15.4%)	37(16.5%)	3(8.3%)	0.20
IHD	117(45.0%)	100(44.6%)	17(47.2%)	0.77
HTN	12(4.6%)	11(4.9%)	1(2.8%)	0.99
Arrhythmia	11(4.2%)	8(3.6%)	3(8.3%)	0.18
Anemia	5(1.9%)	5(2.2%)	0(0.0%)	0.99
Renal failure	9(3.5%)	8(3.6%)	1(2.8%)	0.99
Clinical and biochemical				

parameters				
HR, b.p.m	94.6±22.3	94.6±21.2	94.7±28.7	0.99
SBP, mmHg	133.6±32.4	134.6±31.9	126.8±35.0	0.19
DBP, mmHg	80.5±19.3	81.0±18.8	77.6±22.4	0.34
LVEF (%)	28.8±7.2	29.0±7.2	27.5±7.4	0.23
BNP, pg/mL	5227±4924	5361±5046	3883±1614	0.52
Creatinin, mmol/L	128.5±121.9	124.9±123.5	151.1±110.2	0.23
Medications				
Carvedilol	100 (38.5%)	84(37.5%)	16(44.4%)	0.42
Bisoprolol	90 (34.6%)	82(36.6%)	8(22.2%)	0.09
Metoprolol	35 (13.5%)	25 (11.2%)	10(27.8%)	0.01
Atenolol	35 (13.5%)	33 (14.7%)	2(5.6%)	0.18
ACE-inhibitors	166(63.8%)	150(67.0%)	16(44.4%)	0.009
ARBs	23(8.8%)	18(8.0%)	5(13.9%)	0.33
Statins	180(69.2%)	154(68.8%)	26(72.2%)	0.67
Aspirin	204(78.5%)	176(78.6%)	28(77.8%)	0.91
VKA	19(7.3%)	16(7.1%)	3(8.3%)	0.73
Ibravadine	7(2.7%)	7(3.1%)	0(0.0%)	0.59
Aldosterone antagonists	45(17.3%)	38(17.0%)	7(19.4%)	0.71
Clopidogrel	81(31.2%)	69(30.8%)	12(33.3%)	0.76
Diuretics	113(43.5%)	98(43.8%)	15(41.7%)	0.81
Inotrops use during hospitalization	51 (19.6%)	32 (14.3%)	19 (52.8%)	<0.001

All values are given as n (%) or mean ±SD. ADNHF = Acute de-novo heart failure, BMI=body mass index, CAD= coronary artery disease, TIAs=transient ischemic attacks, CKD=chronic kidney disease, HR=heart rate, SBP= systolic blood pressure, DBP= diastolic blood pressure, LVEF = Left ventricular ejection fraction, VKA= Vitamin K antagonists, ARBs= Angiotensin receptor blockers.

Supplementary table 3: Variables after propensity score matching on inotrops in patients with acute decompensated chronic heart failure, a left ventricular ejection fraction <40% and on beta-blockers on admission.

	Beta-blockers continued N=92	**Beta-blockers withdrawn N=92**	**p value**
Age (years)	60.3±12.7	60.3±15.8	0.98
Male gender	74 (80.4%)	62(67.4%)	0.044*
Noncompliance with medication	51 (55.4%)	19 (20.7%)	<0.001*
SBP, mmHg	147.5±39.8	114.2±31.3	<0.001*
DBP, mmHg	95.9±23.4	67.8±17.2	<0.001*
LVEF (%)	28.3±6.7	25.6±7.6	0.011*
Creatinin, mmol/L	126.7±103.4	158.5±141.4	0.08
Statins	79 (85.9%)	57(62.0%)	<0.001*
Aspirin	92 (100.0%)	64(69.6%)	<0.001*
Inotrops	46 (50.0%)	46 (50.0%)	1.000

All values are given as n (%) or mean ±SD. SBP= systolic blood pressure, DBP= diastolic blood pressure, LVEF = Left ventricular ejection fraction.

Supplementary table 4: Variables after propensity score matching on inotrops in patients with acute de-novo heart failure, a left ventricular ejection fraction LVEF <40% and on beta-blockers on admission.

	Beta-blockers continued N=36	**Beta-blockers withdrawn n=36**	**p value**
Age	59.9±12.7	57.9±13.9	0.514
Gender	11 (30.6%)	10 (27.8%)	0.795
ACE-inhibitors	25 (69.4%)	16 (44.4%)	0.032*
Inotrops	19 (52.8%)	19 (52.8%)	1.000

All values are given as n (%) or mean ±SD.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract- done page 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found- done page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported- done page 4
Objectives	3	State specific objectives, including any prespecified hypotheses- done page 4
Methods		
Study design	4	Present key elements of study design early in the paper- done page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection- done page 5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up- done page 5 *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls- not applicable *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants. not applicable
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed, not applicable *Case-control study*—For matched studies, give matching criteria and the number of controls per case- not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable-done page 5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group-done page 5
Bias	9	Describe any efforts to address potential sources of bias-done page 6
Study size	10	Explain how the study size was arrived at-done page 5 to 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why-done page 6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding- done page 6
		(*b*) Describe any methods used to examine subgroups and interactions-done page 6
		(*c*) Explain how missing data were addressed-done page 6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed- done page 7 *Case-control study*—If applicable, explain how matching of cases and controls was addressed not applicable *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy not applicable
		(*e*) Describe any sensitivity analyses-done page 6

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed- page 6
		(b) Give reasons for non-participation at each stage- page 6-7
		(c) Consider use of a flow diagram- not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders- done page 6-7 and table 1
		(b) Indicate number of participants with missing data for each variable of interest- done page 6-7
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)- done page 7-8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time- done table 2 and 4
		Case-control study—Report numbers in each exposure category, or summary measures of exposure-not applicable.
		Cross-sectional study—Report numbers of outcome events or summary measures-not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included- done page 6 to 8
		(*b*) Report category boundaries when continuous variables were categorized- done page 6 to 8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses- done page 7-8
Discussion		
Key results	18	Summarise key results with reference to study objectives- done page 8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias - done page 10.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence- done pages from 8 to 10
Generalisability	21	Discuss the generalisability (external validity) of the study results-done page 10
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based- done page 13.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Non-withdrawal of beta-blockers in acute decompensated chronic and de-novo heart failure in a prospective multicenter study of patients with acute heart failure in the Middle East.

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Non-withdrawal of beta-blockers in acute decompensated chronic and de-novo heart failure in a prospective multicenter study of patients with acute heart failure in the Middle East.

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Abstract

Objectives: Beta-blockers reduce mortality in heart failure (HF). However, it is not clear whether they should be temporarily withdrawn during acute HF.

Design: Analysis of prospectively collected data

Setting: The GULF-CARE (Gulf aCute heArt failuRe rEgistry) is a prospective multicenter study of patients hospitalized with acute HF in 7 Middle Eastern countries.

Participants: 5005 patients with acute HF.

Outcome measures: We studied the effect of beta-blockers non-withdrawal on intra-hospital, 3-month and 12-month mortality and hospitalization for HF in patients with acute decompensated chronic heart failure (ADCHF) and acute de-novo heart failure (ADNHF), and a LVEF < 40%.

Results: 44.1% of patients were already on beta-blockers on inclusion. Among those, 57.8% had a LVEF <40%. Further, 79.9% were diagnosed with ADCHF and 20.4% with ADNHF. Mean age was 61 (13.9) in the ADCHF group and 59.8 (13.8) in the ADNHF group. Ischemic heart disease was the precipitating factor in 20% of the ADCHF group and 45% in the ADNHF. Intra-hospital mortality was lower in patients whose beta-blocker therapy was not withdrawn in both the ADCHF and ADNHF groups. This protective effect persisted after multivariate analysis (OR 0.05, 95% CI [0.02-0.11]; OR 0.04, 95% CI [0.01-0.16]; respectively, p<0.001 for both) and propensity score matching (OR 0.08, 95% CI [0.01-0.46]; OR 0.04, 95% CI [0.01-0.16]; respectively, p<0.006 for both). At 3 months, mortality was still lower only in ADCHF patients in whom beta-blockers were maintained during initial hospitalization. However, the benefit was lost after correcting for confounding factors. Interestingly, hospitalization for HF and length of hospital stay were unaffected by beta-blockers discontinuation in all patients.

Conclusion: In summary, non-withdrawal of beta-blockers in acute decompensated chronic heart failure and acute de-novo heart failure is associated with lower intra-hospital mortality.

Trial registration number: NCT01467973.

Keywords

Heart failure

Beta-blockers

Acute decompensated chronic heart failure

Acute de-novo heart failure

Strengths and limitations of this study

This is the first study to assess non-withdrawal of beta-blockers in de-novo heart failure.

Like any observational study, selection bias could exist. Moreover, the decision of beta-blocker withdrawal during acute heart failure could have been due to different factors that we did not account for in our analysis.

Furthermore, no information was available regarding the dose of beta-blockers, in particular whether the dose was reduced in patients who continued to use beta-blockers during acute decompensation.

Introduction

Since the publication of the MERIT-HF, CIBIS-II, US Carvedilol Heart failure and COPERNICUS trials[1-4], in which beta-blockers improved survival in heart failure (HF) patients, international guidelines recommended using this drug class as first-line treatment in chronic HF along with the renin-angiotensin system blockers[5]. Initial safety concerns regarding the use of beta-blockers in patients with HF were dropped with the emergence of several studies that demonstrated up to 30% decrease in mortality risk in those patients[6]. Despite the improvement in the treatment and prognosis of chronic HF, acute HF remains a challenging condition, treatment of which is essentially symptomatic. In the EuroHeart Failure Survey II, in-hospital mortality of patients with acute HF was about 7%[7], and one-year mortality above 20%[8]. The continuation of beta-blockers during acute HF remains controversial and subject to clinical judgment. The Beta-blocker CONtinuation Vs. INterruption in patients with Congestive heart failure hospitalizED for a decompensation episode (B-CONVINCED) trial, a randomized, controlled, open-labeled study that compared continuation *versus* withdrawal of beta-blockers during acute HF did not report any short-term or long-term benefit in patients assigned to continue their treatment[9]. In a post-hoc analysis of the Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) study that had a similar design to B-CONVINCED, 1-month and 3-month mortality decreased in patients whose beta-blockers were not withdrawn during initial hospitalization[10]. However, the protective effect was lost after correcting for classical heart failure covariates.

Currently, there is no large-scale data from the Middle East (ME) with regard to beta-blockers use in HF. The aim of this paper is to report on use of beta-blockers in patients admitted with acute HF and to assess short-term and long-term consequences of withdrawal or continuation of beta-blockers in HF patients with left ventricular dysfunction in the ME.

Methods

The Gulf CARE (Gulf aCute heArt failuRe registry) is a multinational multicenter prospective observational acute heart failure survey based on cases admitted to various hospitals in 7 countries from the Gulf Middle East, namely Oman, Saudi Arabia, United Arab Emirates (UAE), Qatar, Bahrain, Yemen, and Kuwait. Details of the recruitment of patients, the study design and methods have been published previously [11 12]. In brief, we collected data, as per the case report form, of patients with acute HF from both genders who were above 18 years of age admitted to the participating hospitals. Recruitment started in February 2012 and ended on November 13, 2012. This was preceded by a pilot phase of 1 month in November 2011. The registry continued to follow-up patients at 3 months and 1 year. The registry protocol was approved by each participating center's research ethics committee or institutional review board (IRB): Directorate of research and studies, Ministry of Health - Sultanate of Oman; King Saud University's IRB, Kingdom of Saudi Arabia; Sheikh Khalifa medical city's IRB, UAE; Hamad Medical Corporation's IRB, Qatar; Mohammed Bin khalifa cardiac center's IRB, Bahrain; Sana'a University' IRB, Yemen and Ministry of health's IRB in Kuwait .The study was registered at clinicaltrials.gov with number NCT01467973. A written informed consent was obtained from all patients

Acute HF was further classified as either acute decompensated chronic heart failure (ADCHF) or acute de-novo heart failure (ADNHF). ADCHF was defined as worsening of HF in patients with a previous diagnosis or hospitalization for HF. ADNHF was defined as acute HF in patients with no prior history of heart failure. All patients were followed-up at 3 months by telephone, and at 1 year either by telephone or by a clinic visit. The registry data was collected on-line using a dedicated Web-site including demographics, risk factors, medical history, clinical manifestations, investigations, medications with dose and management. The participating hospitals ranged from secondary care hospitals to tertiary care hospitals with interventional facilities including device therapy.

The inclusion criteria for this analysis was those patients who were on beta-blockers at time of admission and had a left ventricular ejection fraction (LVEF) < 40%. Those patients with preserved left ventricular function and not on beta-blockers at time of admission were excluded from further analysis. Furthermore, 2 cohorts were created, the first with ADCHF and the second with ADNHF. The main outcome measures were mortality, hospitalization for HF, and length of hospital stay. A scheme of the current prospective trial is described in figure 1.

Baseline categorical variables and outcome measures were summarized using frequency distributions whiles means and standard deviations were used for numeric variables. Outcome measures and baseline patients' characteristics were compared between the two groups: withdrawal and non-withdrawal of beta-blockers using the Chi-squared test (or Fisher's exact test when expected cell counts fell below 5) for categorical variables and the student's t test or Wilcoxon rank sum test for numeric variables. Multivariate logistic regression analysis performed for in-hospital and 3-months included variables that were significantly different between the two groups in addition to age and gender. Adjusted Odds Ratios (OR) and 95% Confidence intervals with p values are presented. All analyses were done separately for the ADCHF and ADNHF patients. In addition, several sensitivity analyses were performed. Propensity scores were computed using logistic regression with membership in the two groups as the outcome and baseline variables that were significantly different between the groups as the independent variables. These scores were used to adjust the association between the mortality outcomes and the main variable (membership in each group) using multivariate logistic regression. Moreover, propensity score matching using the most influential variable (inotropes) was used and the main comparison between the two groups was assessed with and without adjustment to variables that were still significantly different between the two groups even after matching. This latter analysis was not done for the ADNHF groups as the sample sizes became small after matching. Statistical significance was set at the 5% level. All analyses were done using IBM-SPSS version 23.0.

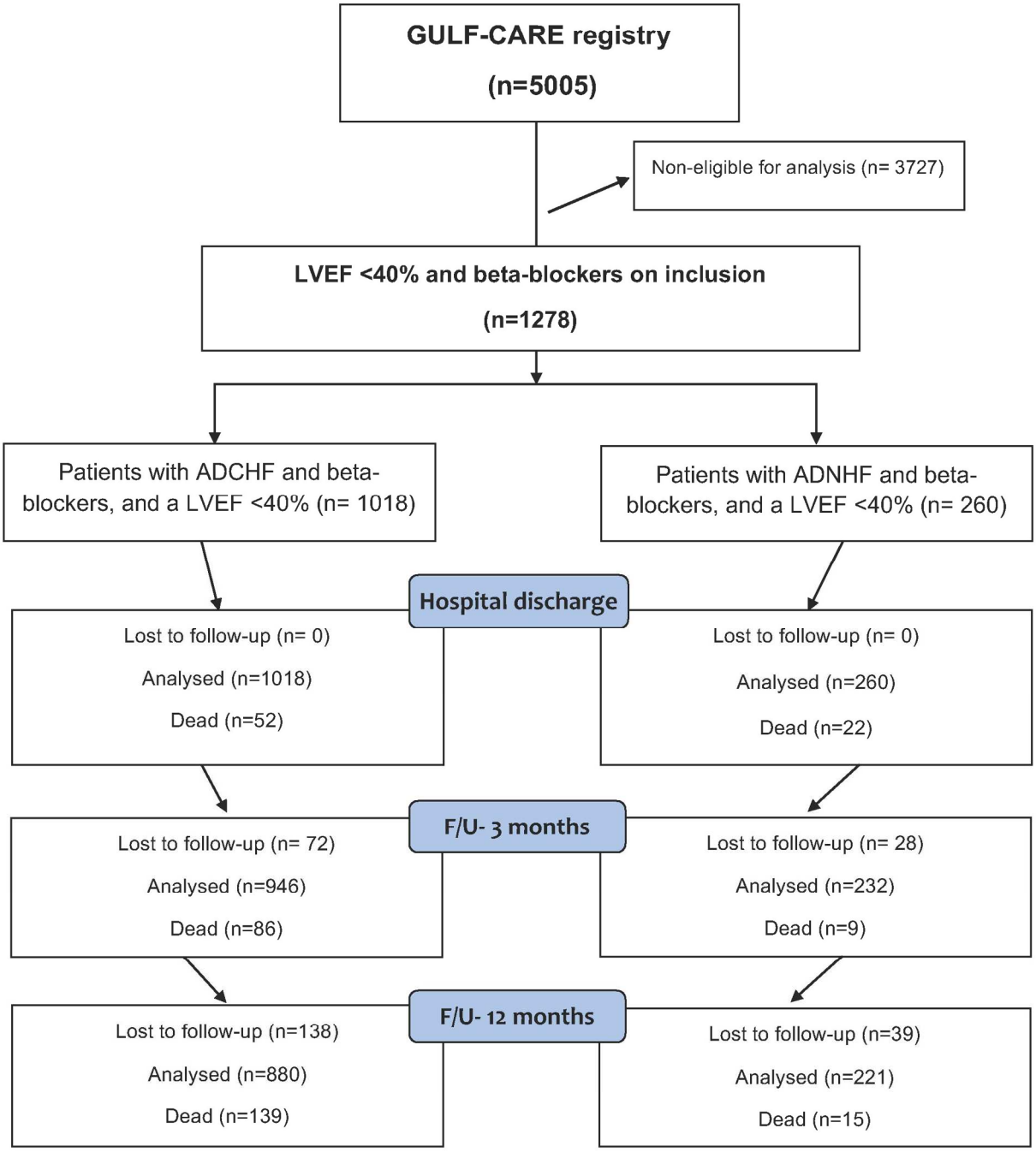

Figure 1: Flow chart of the current prospective analysis. 1278 patients with a LVEF <40% and beta-blockers on admission were analyzed from the 5005 participants in the GULF-CARE registry. ADCHF = Acute decompensated chronic heart failure, ADNHF = Acute de-novo heart failure, LVEF = Left ventricular ejection fraction. F/U = Follow-up.

Results:

Out of the total 5005 participants in the GULF-CARE, 2208 (44.1%) patients were already on beta-blockers on inclusion. Further, beta-blockers were prescribed in 1278 (42.2%) patients with a LVEF <40%. Among those, 1018 (79.9%) were diagnosed with acute decompensated chronic HF (ADCHF) and 260 (20.4%) with acute do-novo heart failure (ADNHF). As shown in table 1, Patients with ADCHF tended to have more comorbidities than patients with ADNHF. They had a higher prevalence of coronary artery disease (CAD), chronic kidney disease (CKD), valvular heart disease, atrial fibrillation (AF) and a lower LVEF; which could explain the more common use of angiotensin receptor antagonists (ARBs), aldosterone antagonists, vitamin K antagonists (VKA) and diuretics in these patients. Interestingly, they smoked less, a phenomenon that could be due to the effect of earlier life-style changes and anti-smoking campaigns in patients with CHF.

Table 1: Baseline characteristics of patients on beta-blockers on admission and a left ventricular ejection fraction <40% included in the Gulf-Care.

	All patients in Gulf Care N=5005	**Patients with a LVEF <40% on beta-blockers on admission N=1278**		**P value ***
		Patients with ADCHF and a LVEF <40%, on beta-blockers on admission. N=1018	**Patients with ADNHF and a LVEF<40%, on beta-blockers on admission. N=260**	
Age (years)	59±15	61.0±13.9	59.8±13.8	0.21
Male gender	3131(62.6%)	751(73.8%)	177(68.1%)	0.07
BMI (kg/m^2)	28±6	27.7±5.8	28.1±5.7	0.26
Hypertension	3059(61.1%)	673(66.1%)	181(69.6%)	0.29
Diabetes Mellitus	2492(49.8%)	569(55.9%)	147(56.5%)	0.86

Hyperlipidemia	1799(35.9%)	464(45.6%)	106(40.8%)	0.16
Smoking	1103(22%)	162(15.9%)	67 (25.8%)	0.001
Race				
Arabs	4516(90.2%)	937 (92.0%)	232(89.2%)	0.04
Asians	473(9.5%)	77(7.6%)	28(10.8%)	
Others	16(0.3%)	4(0.4%)	-	
Past – medical history				
Known CAD	2337(46.7%)	676(66.4%)	150(57.7%)	0.008
Stroke /TIAs	404(8%)	96(9.4%)	29(11.2%)	0.40
Valvular heart disease	675(13.5%)	154(15.1%)	19(7.3%)	0.001
Atrial fibrillation	607(12%)	170(16.7%)	23(8.8 %)	0.001
CKD	744(14.9%)	215(21.1%)	28(10.8%)	0.001
Etiology				
Non-Compliance Medication	964(19%)	300(29.5%)	40(15.4%)	0.05
IHD	1365(27%)	204(20,0%)	117(45.0%)	0.67
HTN	410(8.2%)	46(4.5%)	12(4.6%)	0.26
Arrhythmia	301(6%)	61(6.0%)	11(4.2%)	0.49
Anemia	143(3.1%)	23(2.3%)	5(1.9%)	0.50
Renal failure	221(4.4%)	58(5.7%)	9(3.5%)	0.19
Clinical and biochemical parameters				
HR, b.p.m	77.6±12.8	94.4±22.4	94.6±22.3	0.92
SBP, mmHg	118±18	126.6±30.6	133.6±32.4	0.002
DBP, mmHg	70±12	76.4±17.9	80.5±19.3	0.001
LVEF (%)	36.9±14	26.6±7.1	28.8±7.2	0.001
BNP, pg/mL	5324±4523	6847±9679	5227±4924	0.21
Creatinine, mmol/L	130±116	137.7±116.3	128.5±121.9	0.24
Medications				

Carvedilol	1099(21.9%)	649(63.8%)	100 (38.5%)	0.001
Bisoprolol	626 (12.5%)	286 (28.1%)	90 (34.6%)	0.04
Metoprolol	299 (5.9%)	64 (6.3%)	35 (13.5%)	0.001
Atenolol	184 (3.6%)	19 (1.9%)	35 (13.5%)	0.001
ACE-inhibitors	2762(55.2%)	652(64.0%)	166(63.8%)	0.96
ARBs	645(12.9%)	180(17.7%)	23(8.8%)	0.001
Statins	2555(51%)	751 (73.8%)	180(69.2%)	0.14
Aspirin	3089(61.7%)	832 (81.7%)	204(78.5%)	0.23
VKA	618(12%)	221(21.7%)	19(7.3%)	0.001
Ibravadine	115(2.3%)	48(4.7%)	7(2.7%)	0.15
Aldosterone antagonists	840(16.8%)	419(41.2%)	45(17.3%)	0.001
Clopidogrel	966(19%)	301(29.6%)	81(31.2%)	0.61
Diuretics	2882(57.6%)	920(90.4%)	113(43.5%)	0.001
Inotropes use during hospitalization	783 (16%)	156 (15.3%)	51 (19.6%)	0.96

All values are given as n (%) or mean ±SD. * p value: patients with acute decompensated chronic heart failure and LVEF <40% on beta-blockers on admission vs. de – Novo heart failure and LVEF <40% on beta-blockers on admission. ADCHF = Acute decompensated chronic heart failure, ADNHF = Acute de-novo heart failure, BMI=body mass index, CAD= coronary artery disease, TIAs=transient ischemic attacks, CKD=chronic kidney disease, HR=heart rate, SBP= systolic blood pressure, DBP= diastolic blood pressure, LVEF = Left ventricular ejection fraction, VKA= Vitamin K antagonists, ARBs= Angiotensin receptor blockers.

Beta-blockers were withdrawn in 10% of the patients in the ADCHF group and 13.8% in the ADNHF group. Those ADCHF patients in whom beta-blockers were discontinued had a lower blood pressure at inclusion and half of them required inotropic support during hospitalization **(supplementary table 1).** ADNHF patients who continued beta-blockade therapy were more commonly prescribed ACE-inhibitors and required less inotropic support **(supplementary table 2).**

In the ADCHF group, 15 (1.6%) in-hospital deaths occurred in patients whose beta-blocker therapy was not withdrawn as compared to 37 (40.2%) when beta-blockers were discontinued (p<0.001) (**Table 2**).

Table 2: Effect of non-withdrawal of beta-blockers in acute decompensated chronic heart failure with beta-blocker therapy on admission and a LVEF <40%

	All patients with acute decompensated heart failure, LVEF <40% and on beta-treatment on admission **N=1018**	**Beta-blockers maintained during hospitalization** **N=926(91%)**	**Beta-blockers withdrawn during hospitalization** **N=92(9.0%)**	**P value**
In–hospital outcome				
Death	52/1018(5.1%)	15/926(1.6%)	37/92(40.2%)	<0.001*
Length of stay	9.9±15.0	9.7±15.1	12.3±13.6	0.1
3-month follow-up				
Death	86/946(9.1%)	77/896(8.6%)	9/50(18.0%)	0.038
Hospitalization for HF	219/859(25.5%)	204/818(24.9%)	15/41(36.6%)	0.09
Length of stay (days)	8.1±7.6	8.1±7.8	7.7±4.3	0.86
12-month follow-up				
Death	139/880(15.8%)	128/835(15.3%)	11/45(24.4%)	0.10
Hospitalization for HF	333/741 (44.9%)	316/707 (44.7%)	17/34 (50.0%)	0.54
Length of stay (days)	9.6±12.0	9.6±12.1	10.9±11.1	0.73

The frequencies and percentages for death, hospitalization for heart failure (HF) and length of stay during hospitalization. Death rates were cumulative. All values are given as n (%) or mean ±SD.

Multivariate analysis showed that age, gender, non-compliance to medication, SBP, DBP, creatinine and statins were not predictors of in-hospital mortality in case of non-withdrawal of beta-blockers. As expected, inotropic use was significantly associated with higher mortality in our model **(Table 3).**

Table 3: Multivariate analysis for intra-hospital and 3-month mortality in patients with ACDHF, a LVEF <40% and beta-blockers on admission.

	Variable	OR	95% .C.I	P value
In-hospital mortality	Age	1.022	0.991-1.055	0.17
	Gender	1.058	0.428-2.618	0.90
	Non-compliance to medication	1.736	0.642-4.698	0.27
	SBP	0.990	0.968-1.014	0.41
	DBP	1.003	0.964-1.044	0.87
	LVEF	1.053	0.998-1.003	0.07
	Creatinine	1.001	0.998-1.001	0.59
	Aspirin	1.357	0.477-3.865	0.56
	Statins	2.083	0.763-5.684	0.15
	Inotropes	20.368	8.241-50.337	<0.001*
	Beta-blockers on discharge			
	Beta-blockers withdrawn (reference group)	1	-	
	Beta-blockers maintained	0.050	0.022-0.112	<0.001*

3-month mortality	Age	1.029	1.010-1.048	0.002*
	Gender	0.974	0.579-1.638	0.92
	Non-compliance to medication	1.267	0.753-2.133	0.37
	SBP	0.993	0.980-1.005	0.26
	DBP	1.005	0.984-1.026	0.66
	LVEF	1.003	0.970-1.037	0.87
	Creatinine	1.001	1.000-1.003	0.15
	Aspirin	1.516	0.828-2.777	0.17
	Statins	1.307	0.747-2.284	0.34
	Inotropes	1.456	0.759-2.793	0.25
	Beta-blockers on discharge			
	Beta-blockers withdrawn (reference group)	1		
	Beta-blockers maintained	0.513	0.231-1.143	0.10

SBP= systolic blood pressure, DBP = diastolic blood pressure, LVEF = Left ventricular ejection fraction.

Nevertheless, non-withdrawal of beta-blockers was associated with less mortality risk even after correcting for all the parameters (OR=0.05, 95% CI: 0.022-0.112, p<0.001). To confirm our findings, we performed a propensity score matching on inotropic use **(supplementary Table 3).** Non-withdrawal of beta-blockers was associated with less mortality in the propensity model (OR=0.05, 95% CI: 0.015-0.170, p<0.001), even after correcting for variables that remained significantly different in the new model (OR=0.084, 95% CI: 0.015-0.468, p=0.005). At 3 months, fewer deaths also occurred in the group of patients whose beta-blockers therapy was not withdrawn (p= 0.038). However, after multivariate logistic regression analysis, the protection conferred by beta-blockade continuation was lost (OR=0.513, 95% CI: 0.231-1.143, p=0.10).

In the ADNHF group, 5 (2.2%) in-hospital deaths occurred in patients whose beta-blocker therapy was not withdrawn as compared to 17 (47.2%) when beta-blockers were discontinued (p<0.001). However, mortality rates were comparable at 3 months and one year **(Table 4).**

Table 4: Effect of non-withdrawal of beta-blockers in acute decompensated de-novo heart failure with beta-blocker therapy on admission and LVEF <40%

	All patients with de-novo heart failure, LVEF <40% and on beta-blockers treatment on admission. **N=260**	**Beta-blockers maintained during hospitalization** **N=224(86.2%)**	**Beta-blockers withdrawn during hospitalization** **N=36(13.8%)**	**p- value**
In–hospital outcome				
Death	22/260(8.5%)	5/224(2.2%)	17/36(47.2%)	<0.001*
Length of stay	9.7±16.1	9.6±16.6	10.1±12.1	0.86
3 months follow-up				
Death	9/232(3.9%)	7/214(3.3%)	2/18(11.1%)	0.14
Hospitalization for HF	39/223(17.5%)	38/207(18.4%)	1/16(6.3%)	0.31
Length of stay	8.8±9.8	8.8±9.9	8.0±NE	NE
At 1 year follow-up				
Death	15/221(6.8%)	13/206(6.3%)	2/15(13.3%)	0.27
Hospitalization for HF	61/206(29.6%)	73/193(37.8%)	3/13(23.1%)	0.38
Length of stay	7.9±7.5	8.2±7.6	2.7±2.1	0.21

The frequencies and percentages for death, hospitalization for heart failure (HF) and length of stay during hospitalization. Death rates were cumulative. All values are given as n(%) or mean ±SD.

Multivariate analysis did not show that age, gender or Ace-inhibitors, which were different among both groups, predicted mortality **(Table 5).**

Table 5: Multivariate analysis for intra-hospital death in patients with ADNHF, a LVEF <40% and beta-blockers on admission

Variable	OR	95 % C.I	P value
Age	1.047	0.992-1.105	0.097
Gender	2.179	0.431-10.989	0.346
ACE-inhibitors	1.112	0.215-5.757	0.899
Inotrops	172.272	16.002-1854.600	<0.001*
Beta-blockers			
Beta-blockers withdrawn (reference group)	1		
Beta-blockers maintained	0.018	0.003-0.122	<0.001*

SBP= systolic blood pressure, DBP = diastolic blood pressure, LVEF = Left ventricular ejection fraction.

Similarly, to the ADCHF, inotropic use was highly associated with mortality. We also performed a propensity score matching on inotropic use **(supplementary Table 4)** and confirmed that beta-blocker continuation in ADNHF has a favorable outcome (OR=0.05, 95% CI: 0.015-0.170, p<0.001), even after correcting for variables that remained significantly different between both groups in the new model (OR=0.047, 95% CI: 0.013-0.169, p<0.001). Similarly to patients with ADCHF, hospitalization for HF and length of stay were unaffected by the withdrawal of beta-blockers.

Discussion

This observational study demonstrates that pursuing beta-blocker therapy during acute HF confers to patients with chronic and de-novo HF cardiovascular protection and decreases mortality. Interestingly, randomized placebo-controlled trials that assessed pursuing beta-blockers versus withdrawal during acute HF are missing; available data are extrapolated from post-hoc analysis. The B-convinced was designed as a non-inferiority trial and demonstrated only safety of beta-blockers during acute decompensation[9]. In a retrospective analysis of the SURVIVE study that initially assessed 2 inotropic treatments in critical patients with acute HF, the benefit associated with non-withdrawal of beta-blockers was lost after correcting for HF covariates; only patients who never received beta-blockers had a worse outcome as compared to patients who were on these drugs at inclusion and on discharge[10]. In a sub-analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization (ESCAPE) that assessed pulmonary artery catheter use among patients admitted with acute HF, patients already prescribed beta-blockers on admission had a lower 6-month mortality risk and a shorter hospitalization stay[13]. Outcomes of the Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF), designed as a randomized placebo-controlled trial, failed to test the superiority of milnirone to placebo in patients with ADCHF[14]. Further observational analysis showed that withdrawal of beta-blockers was associated with a greater risk of 2-month mortality and re-hospitalization for HF despite limitations due to the use of milnirone in those patients and the small number of patients analyzed[15].

Our results are comparable to previous observational studies from North America and Europe. In the Italian Survey on Acute Heart Failure, withdrawal of beta-blockers during acute HF was associated with almost 4-fold increase in the risk of intra-hospital mortality[16]. The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) is one of the largest Northern American registries of patients admitted with acute HF. Maintenance of beta-blockers during

acute decompensation was associated with better outcome in post-discharge mortality[17]. Consistent with our findings, Prins et al reported in a recent meta-analysis that included over 2700 patients treated with beta-blockers and hospitalized for acute HF, that withdrawal of beta-blockers significantly increased in-hospital and short term mortality, and re-hospitalization for HF [18].

Despite firm safety data and un-doubted long-term benefit, beta-blocker therapy remains under-prescribed. In our study, only 44.1% of all patients presenting with acute HF and 44.2 % of patients with a LVEF<40% were treated with beta-blockers. The frequency of beta-blockers prescription is variable according to cohorts and ranges from 32% in the "Italian Survey on Acute Heart Failure" study [16] to 53.3% in the SURVIVE study[10] and 62% in the ESCAPE trial [13].

It is not known why withdrawal of beta-blockers in acute HF is associated with a worse prognosis. Activation of the sympathetic system, increase of catecholamine levels and alterations in cardiac β-receptors are the hallmark of chronic HF; therefore beta-blocker therapy in chronic HF could limit the deleterious effect of chronic β-receptor stimulation such as arrhythmias, hypertrophy and cardiomyocytes apoptosis[19]. It may be possible that withdrawal of beta-blockers in the acute phase takes away earlier protective effect of beta-adrenergic inhibition at a time when the neuro-hormonal system is activated and catecholamines are significantly increased[20].

Managing beta-blockers during acute HF is still unclear to most physicians. The Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial investigators were the first to report that in-hospital initiation of beta-blockers was safe compared to post-discharge[21]. The latest guidelines from both the Society of Cardiology (ESC)[22] and the American college of Cardiology foundation (ACCF)/American heart association (AHA) [23] recommend initiating a beta-blocker therapy following acute HF as soon as the patient is stable and before discharge. However, uncertainty persists in regards to continuing beta-blockers during an acute decompensation. Beta-blockade therapy discontinuation during AHF is variable. In older studies such as the OPTIME-CHF, beta-blockers were

withdrawn in over 20% of patients [15]. In our study, beta-blockers were withdrawn in 10% of patients with ADCHF and 13.8% of patients with ADNHF. Those numbers are almost similar to the Italian Survey on Acute Heart Failure in which Orso et al reported a withdrawal rate of 9% in all AHF patients with beta-blockers on admission [16] However, Bohm et al reported a lower rate (6.8%) in the retrospective analysis of the SURVIVE study[10].

It is not known why mortality risk reduction extends up to 3 months in ADCHF but not in ADNHF although the first group has higher cardiovascular comorbidities and more severe risk factors. One explanation could be the higher prescription of cardioprotective drugs such as ACE inhibitors, ARBs, diuretics; all having shown to reduce mortality in patients with chronic HF and improve the outcome [24-26]. One other explanation would also be the frequent use of beta-blockers approved for HF in patients with ADCHF whereas the prescription of non-HF selective beta-blockers such as atenolol was more common in ADNHF. Finally, we cannot rule out that the relatively small number of patients with ADNHF, coupled to an even smaller death rate at 3 months, does not enable us draw any meaningful conclusions on long-term mortality in those patients.

Our study has a few limitations. Like any observational study, selection bias could exist. The decision of beta-blocker withdrawal during acute HF could have been to different factors not accounted for in our analysis. Beta-blocker therapy could have been withdrawn in the more severe patients with a poor prognosis. Despite the correction on available cofounding factors, we could have missed other markers of disease severity that were not recorded in the cohort. In addition, we could not determine whether the dosage of beta-blockers on admission, or any reduction during hospitalization, might have influenced the outcome. Finally, the duration of beta-blocker treatment prior to acute HF was not recorded; this variable could also be a confounding factor since long-term beta-blocker treatment could have been more beneficial than short-term.

Conclusion

Our study suggests non-withdrawal of beta-blocker therapy during acute heart failure reduces short-term mortality risk in patients with acute decompensated chronic and de-novo heart failure; findings that could only be validated in randomized controlled trials designed to show the superiority of non-withdrawal of beta-blockade therapy and also determine whether beta-blocker dose should be reduced or kept unchanged compared to a withdrawal strategy.

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Footnotes

Contribution: KS, KFA, NA, AA-A, MA-J, BB, WA, MR, NB, HA, AA-M, HAF, AE, PP and JAS were involved in the design of the Gulf CARE registry and patient enrolment and ensuring quality control of the study. CAK designed the analysis and wrote the manuscript. ZM and RS carried out the statistical analyses. All authors approved the final version of the manuscript.

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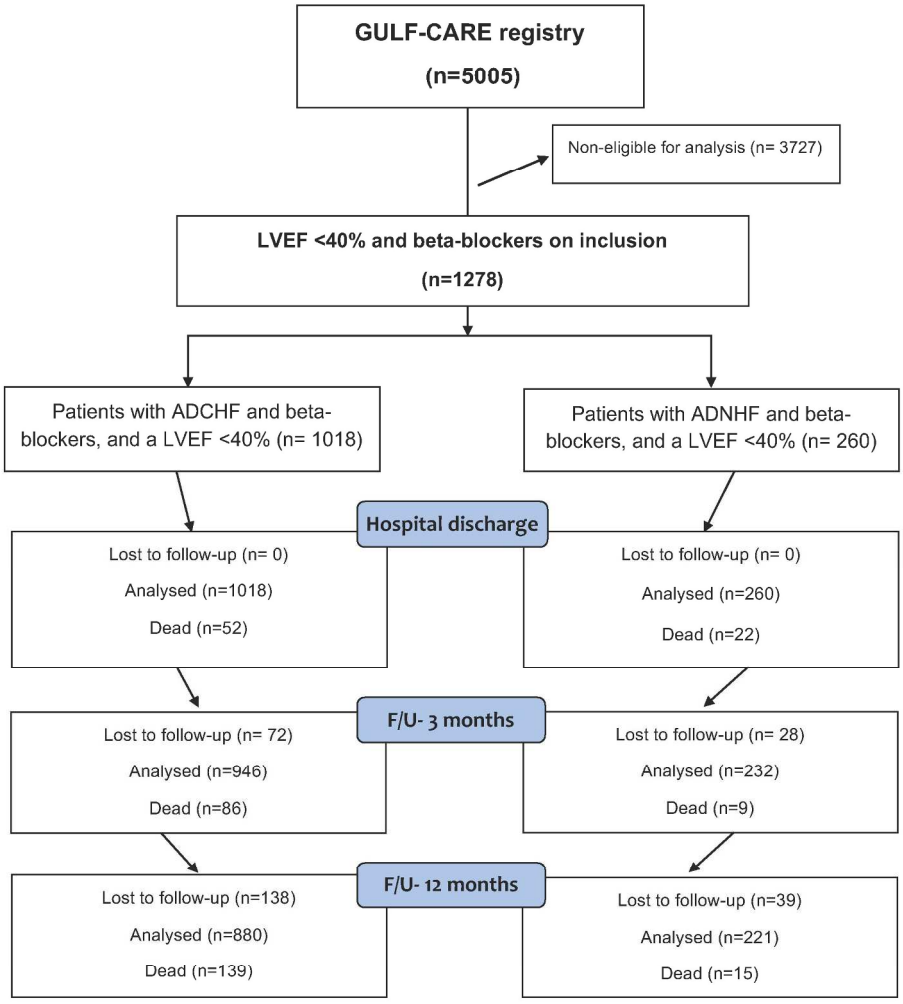

Figure 1: Flow chart of the current prospective analysis. 1278 patients with a LVEF <40% and beta-blockers on admission were analyzed from the 5005 participants in the GULF-CARE registry. ADCHF = Acute decompensated chronic heart failure, ADNHF = Acute de-novo heart failure, LVEF = Left ventricular ejection fraction, F/U= Follow-up.

211x230mm (300 x 300 DPI)

Supplementary table 1: Baseline characteristics of patients with acute decompensated chronic heart failure and a left ventricular ejection fraction <40%, on beta-blockers on admission

	Patients with ADCHF with a LVEF <40% and beta-blockers on admission N=1018	**Beta-blockers maintained during hospitalization N=926**	**Beta-blockers withdrawn during hospitalization N=92**	**p value**
Age (years)	61.0±13.9	61.1±13.7	60.3±15.8	0.64
Male gender	751(73.8%)	689(74.4%)	62(67.4%)	0.14
BMI (kg/m^2)	27.7±5.8	27.6±5.8	28.3±5.7	0.28
Hypertension	673(66.1%)	620(67.0%)	53(57.6%)	0.07
Diabetes Mellitus	569(55.9%)	518(55.9%)	51(55.4%)	0.92
Hyperlipidemia	464(45.6%)	419(45.2%)	45(48.9%)	0.50
Smoking	162(15.9%)	149(16.1%)	13(14.1%)	0.62
Race				
Arabs	937 (92.0%)	852(92.0%)	85(92.4%)	0.37
Asians	77(7.6%)	71(7.7%)	6(6.5%)	
Others	4(0.4%)	3(0.3%)	1(1.1%)	
Past – medical history				
Known CAD	676(66.4%)	617(66.6%)	59(64.1%)	0.62
Stroke /TIAs	96(9.4%)	89(9.6%)	7(7.6%)	0.53
Valvular heart disease	154(15.1%)	139(15.0%)	15(16.3%)	0.74
Atrial fibrillation	170(16.7%)	157(17.0%)	13(14.1%)	0.48
CKD	215(21.1%)	192(20.7%)	23(25.0%)	0.33
Etiology				
Non-Compliance Medication	300(29.5%)	281(30.3%)	19(20.7%)	0.052
IHD	204(20,0%)	184(19.9%)	20(21.7%)	0.66
HTN	46(4.5%)	44(4.8%)	2(2.2%)	0.42
Arrhythmia	61(6.0%)	57(6.2%)	4(4.3%)	0.48
Anemia	23(2.3%)	20(2.2%)	3(3.3%)	0.45
Renal failure	58(5.7%)	50(5.4%)	8(8.7%)	0.19
Clinical and biochemical parameters				

HR, b.p.m	94.4±22.4	94.8±22.5	91.1±21.2	0.14
SBP, mmHg	126.6±30.6	127.8±30.3	114.2±31.3	<0.001
DBP, mmHg	76.4±17.9	77.2±17.8	67.8±17.2	<0.001
LVEF (%)	26.6±7.1	26.7±7.1	25.6±7.6	0.16
BNP, pg/mL	6847±9679	6851±9831	6777±7271	0.97
Creatinin, mmol/L	137.7±116.3	135.7±113.4	158.5±141.4	0.07
Medications				
Carvedilol	649(63.8%)	589 (63.6%)	60(65.2%)	0.75
Bisoprolol	286 (28.1%)	265(28.6%)	21(22.8%)	0.23
Metoprolol	64 (6.3%)	57(6.2%)	7(7.6%)	0.58
Atenolol	19 (1.9%)	15(1.6%)	4(4.3%)	0.08
ACE-inhibitors	652(64.0%)	600(64.8%)	52(56.5%)	0.11
ARBs	180(17.7%)	167 (18.0%)	13(14.1%)	0.34
Statins	751 (73.8%)	694(74.9%)	57(62.0%)	0.007
Aspirin	832 (81.7%)	768(82.9%)	64(69.6%)	0.002
VKA	221(21.7%)	196 (21.2%)	25(27.2%)	0.18
Ibravadine	48(4.7%)	42 (4.5%)	6(6.5%)	0.43
Aldosterone antagonists	419(41.2%)	383 (41.4%)	36 (39.1%)	0.67
Clopidogrel	301(29.6%)	274 (29.6%)	27(29.3%)	0.96
Diuretics	920(90.4%)	835(90.2%)	85(92.4%)	0.49
Inotrops use during hospitalization	156 (15.3%)	110 (11.9%)	46 (50.0%)	<0.001*

All values are given as n (%) or mean ±SD. ADCHF = Acute decompensated chronic heart failure, BMI=body mass index, CAD= coronary artery disease, TIAs=transient ischemic attacks, CKD=chronic kidney disease, HR=heart rate, SBP= systolic blood pressure, DBP= diastolic blood pressure, LVEF = Left ventricular ejection fraction, VKA= Vitamin K antagonists, ARBs= Angiotensin receptor blockers.

Supplementary table 2: Baseline characteristics of patients with acute de-novo heart failure and a left ventricular ejection fraction <40%, on beta-Blockers on admission.

	Patients with ADCHF with a LVEF <40% and beta-blockers on admission N=260	**Beta-blockers maintained during hospitalization N=224**	**Beta-blockers withdrawn during hospitalization N=36**	**p**
Age (years)	59.8±13.8	60.1±13.8	57.9±13.9	0.35
Male gender	177(68.1%)	151(67.4%)	26(72.2%)	0.56
BMI (kg/m^2)	28.1±5.7	28.1±5.8	28.1±5.2	0.99
Hypertension	181(69.6%)	158(70.5%)	23(63.9%)	0.42
Diabetes Mellitus	147(56.5%)	123(54.9%)	24(66.7%)	0.18
Hyperlipidemia	106(40.8%)	92(41.1%)	14(38.9%)	0.80
Smoking	67 (25.8%)	60(26.8%)	7(19.4%)	0.35
Race				
Arabs	232(89.2%)	201 (89.7%)	31(86.1%)	0.56
Asians	28(10.8%)	23(10.3%)	5(13.9%)	
Others	-	-	-	
Past – medical history				
Known CAD	150(57.7%)	130(58.0%)	20(55.6%)	0.78
Stroke /TIAs	29(11.2%)	24(10.7%)	5(13.9%)	0.57
Valvular heart disease	19(7.3%)	16(7.1%)	3 (8.3%)	0.73
Atrial fibrillation	23(8.8 %)	19(8.5%)	4(11.1%)	0.53
CKD	28(10.8%)	22(9.8%)	6 (16.7%)	0.24
Etiology				
Non-Compliance Medication	40(15.4%)	37(16.5%)	3(8.3%)	0.20
IHD	117(45.0%)	100(44.6%)	17(47.2%)	0.77
HTN	12(4.6%)	11(4.9%)	1(2.8%)	0.99
Arrhythmia	11(4.2%)	8(3.6%)	3(8.3%)	0.18
Anemia	5(1.9%)	5(2.2%)	0(0.0%)	0.99
Renal failure	9(3.5%)	8(3.6%)	1(2.8%)	0.99
Clinical and biochemical				

parameters				
HR, b.p.m	94.6±22.3	94.6±21.2	94.7±28.7	0.99
SBP, mmHg	133.6±32.4	134.6±31.9	126.8±35.0	0.19
DBP, mmHg	80.5±19.3	81.0±18.8	77.6±22.4	0.34
LVEF (%)	28.8±7.2	29.0±7.2	27.5±7.4	0.23
BNP, pg/mL	5227±4924	5361±5046	3883±1614	0.52
Creatinin, mmol/L	128.5±121.9	124.9±123.5	151.1±110.2	0.23
Medications				
Carvedilol	100 (38.5%)	84(37.5%)	16(44.4%)	0.42
Bisoprolol	90 (34.6%)	82(36.6%)	8(22.2%)	0.09
Metoprolol	35 (13.5%)	25 (11.2%)	10(27.8%)	0.01
Atenolol	35 (13.5%)	33 (14.7%)	2(5.6%)	0.18
ACE-inhibitors	166(63.8%)	150(67.0%)	16(44.4%)	0.009
ARBs	23(8.8%)	18(8.0%)	5(13.9%)	0.33
Statins	180(69.2%)	154(68.8%)	26(72.2%)	0.67
Aspirin	204(78.5%)	176(78.6%)	28(77.8%)	0.91
VKA	19(7.3%)	16(7.1%)	3(8.3%)	0.73
Ibravadine	7(2.7%)	7(3.1%)	0(0.0%)	0.59
Aldosterone antagonists	45(17.3%)	38(17.0%)	7(19.4%)	0.71
Clopidogrel	81(31.2%)	69(30.8%)	12(33.3%)	0.76
Diuretics	113(43.5%)	98(43.8%)	15(41.7%)	0.81
Inotrops use during hospitalization	51 (19.6%)	32 (14.3%)	19 (52.8%)	<0.001

All values are given as n (%) or mean ±SD. ADNHF = Acute de-novo heart failure, BMI=body mass index, CAD= coronary artery disease, TIAs=transient ischemic attacks, CKD=chronic kidney disease, HR=heart rate, SBP= systolic blood pressure, DBP= diastolic blood pressure, LVEF = Left ventricular ejection fraction, VKA= Vitamin K antagonists, ARBs= Angiotensin receptor blockers.

Supplementary table 3: Variables after propensity score matching on inotrops in patients with acute decompensated chronic heart failure, a left ventricular ejection fraction <40% and on beta-blockers on admission.

	Beta-blockers continued N=92	**Beta-blockers withdrawn N=92**	**p value**
Age (years)	60.3±12.7	60.3±15.8	0.98
Male gender	74 (80.4%)	62(67.4%)	0.044*
Noncompliance with medication	51 (55.4%)	19 (20.7%)	<0.001*
SBP, mmHg	147.5±39.8	114.2±31.3	<0.001*
DBP, mmHg	95.9±23.4	67.8±17.2	<0.001*
LVEF (%)	28.3±6.7	25.6±7.6	0.011*
Creatinin, mmol/L	126.7±103.4	158.5±141.4	0.08
Statins	79 (85.9%)	57(62.0%)	<0.001*
Aspirin	92 (100.0%)	64(69.6%)	<0.001*
Inotrops	46 (50.0%)	46 (50.0%)	1.000

All values are given as n (%) or mean ±SD. SBP= systolic blood pressure, DBP= diastolic blood pressure, LVEF = Left ventricular ejection fraction.

Supplementary table 4: Variables after propensity score matching on inotrops in patients with acute de-novo heart failure, a left ventricular ejection fraction LVEF <40% and on beta-blockers on admission.

	Beta-blockers continued N=36	**Beta-blockers withdrawn n=36**	**p value**
Age	59.9±12.7	57.9±13.9	0.514
Gender	11 (30.6%)	10 (27.8%)	0.795
ACE-inhibitors	25 (69.4%)	16 (44.4%)	0.032*
Inotrops	19 (52.8%)	19 (52.8%)	1.000

All values are given as n (%) or mean ±SD.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract- done page 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found- done page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported- done page 4
Objectives	3	State specific objectives, including any prespecified hypotheses- done page 4
Methods		
Study design	4	Present key elements of study design early in the paper- done page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection- done page 5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up- done page 5 *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls- not applicable *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants. not applicable
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed, not applicable *Case-control study*—For matched studies, give matching criteria and the number of controls per case- not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable-done page 5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group-done page 5
Bias	9	Describe any efforts to address potential sources of bias-done page 6
Study size	10	Explain how the study size was arrived at-done page 5 to 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why-done page 6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding- done page 6
		(*b*) Describe any methods used to examine subgroups and interactions-done page 6
		(*c*) Explain how missing data were addressed-done page 6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed- done page 7 *Case-control study*—If applicable, explain how matching of cases and controls was addressed not applicable *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy not applicable
		(*e*) Describe any sensitivity analyses-done page 6

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed- page 6
		(b) Give reasons for non-participation at each stage- page 6-7
		(c) Consider use of a flow diagram- not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders- done page 6-7 and table 1
		(b) Indicate number of participants with missing data for each variable of interest- done page 6-7
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)- done page 7-8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time- done table 2 and 4
		Case-control study—Report numbers in each exposure category, or summary measures of exposure-not applicable.
		Cross-sectional study—Report numbers of outcome events or summary measures-not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included- done page 6 to 8
		(*b*) Report category boundaries when continuous variables were categorized- done page 6 to 8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses- done page 7-8
Discussion		
Key results	18	Summarise key results with reference to study objectives- done page 8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias - done page 10.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence- done pages from 8 to 10
Generalisability	21	Discuss the generalisability (external validity) of the study results-done page 10
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based- done page 13.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Non-withdrawal of beta-blockers in acute decompensated chronic and de-novo heart failure with reduced ejection fraction in a prospective multicenter study of patients with acute heart failure in the Middle East

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Non-withdrawal of beta-blockers in acute decompensated chronic and de-novo heart failure with reduced ejection fraction in a prospective multicenter study of patients with acute heart failure in the Middle East.

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Abstract

Objectives: Beta-blockers reduce mortality in heart failure (HF). However, it is not clear whether they should be temporarily withdrawn during acute HF.

Design: Analysis of prospectively collected data

Setting: The GULF-CARE (Gulf aCute heArt failuRe rEgistry) is a prospective multicenter study of patients hospitalized with acute HF in 7 Middle Eastern countries.

Participants: 5005 patients with acute HF.

Outcome measures: We studied the effect of beta-blockers non-withdrawal on intra-hospital, 3-month and 12-month mortality and re-hospitalization for HF in patients with acute decompensated chronic heart failure (ADCHF) and acute de-novo heart failure (ADNHF), and a LVEF < 40%.

Results: 44.1% of patients were already on beta-blockers on inclusion. Among those, 57.8% had a LVEF <40%. Further, 79.9% were diagnosed with ADCHF and 20.4% with ADNHF. Mean age was 61 (SD 13.9) in the ADCHF group and 59.8 (SD 13.8) in the ADNHF group. Intra-hospital mortality was lower in patients whose beta-blocker therapy was not withdrawn in both the ADCHF and ADNHF groups. This protective effect persisted after multivariate analysis (OR 0.05, 95% CI [0.022-0.112]; OR 0.018, 95% CI [0.003-0.122]; respectively, p<0.001 for both) and propensity score matching even after correcting for variables that remained significant in the new model (OR 0.084, 95% CI [0.015-0.468], p=0.005; OR 0.047, 95% CI [0.013-0.169], p<0.001; respectively). At 3 months, mortality was still lower only in ADCHF patients in whom beta-blockers were maintained during initial hospitalization. However, the benefit was lost after correcting for confounding factors. Interestingly, re-hospitalization for HF and length of hospital stay were unaffected by beta-blockers discontinuation in all patients.

Conclusion: In summary, non-withdrawal of beta-blockers in acute decompensated chronic and de-novo heart failure with reduced ejection fraction is associated with lower intra-hospital mortality, but does influence 3- and 12- month mortality, re-hospitalization for heart failure, and the length of hospital stay.

Trial registration number: NCT01467973.

Keywords

Heart failure

Beta-blockers

Acute decompensated chronic heart failure

Acute de-novo heart failure

Cardiovascular disease

Strengths and limitations of this study

This is the first study to assess non-withdrawal of beta-blockers in de-novo heart failure.

Like any observational study, selection bias could exist. Moreover, the decision of beta-blocker withdrawal during acute heart failure could have been due to different factors that we did not account for in our analysis.

Furthermore, no information was available regarding the dose of beta-blockers, in particular whether the dose was reduced in patients who continued to use beta-blockers during acute decompensation.

Introduction

Since the publication of the MERIT-HF, CIBIS-II, US Carvedilol Heart failure and COPERNICUS trials[1-4], in which beta-blockers improved survival in heart failure (HF) patients, international guidelines recommended using this drug class as first-line treatment in chronic HF along with the renin-angiotensin system blockers[5]. Initial safety concerns regarding the use of beta-blockers in patients with HF were dropped with the emergence of several studies that demonstrated up to 30% decrease in mortality risk in those patients[6]. Despite the improvement in the treatment and prognosis of chronic HF, acute HF remains a challenging condition, treatment of which is essentially symptomatic. In the EuroHeart Failure Survey II, in-hospital mortality of patients with acute HF was about 7%[7], and one-year mortality above 20%[8]. The continuation of beta-blockers during acute HF remains controversial and subject to clinical judgment. The Beta-blocker CONtinuation Vs. INterruption in patients with Congestive heart failure hospitalizED for a decompensation episode (B-CONVINCED) trial, a randomized, controlled, open-labeled study that compared continuation *versus* withdrawal of beta-blockers during acute HF did not report any short-term or long-term benefit in patients assigned to continue their treatment[9]. In a post-hoc analysis of the Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) study that had a similar design to B-CONVINCED, 1-month and 3-month mortality decreased in patients whose beta-blockers were not withdrawn during initial hospitalization[10]. However, the protective effect was lost after correcting for classical heart failure covariates.

Currently, there is no large-scale data from the Middle East (ME) with regard to beta-blockers use in HF. The aim of this paper is to report on use of beta-blockers in patients admitted with acute HF and to assess short-term and long-term consequences of withdrawal or continuation of beta-blockers in HF patients with left ventricular dysfunction in the ME.

Methods

The Gulf CARE (Gulf aCute heArt failuRe registry) is a multinational multicenter prospective observational acute heart failure survey based on cases admitted to various hospitals in 7 countries from the Gulf Middle East, namely Oman, Saudi Arabia, United Arab Emirates (UAE), Qatar, Bahrain, Yemen, and Kuwait. Details of the recruitment of patients, the study design and methods have been published previously [11 12]. In brief, we collected data, as per the case report form, of patients with acute HF from both genders who were above 18 years of age admitted to the participating hospitals. Recruitment started in February 2012 and ended on November 13, 2012. This was preceded by a pilot phase of 1 month in November 2011. The registry continued to follow-up patients at 3 months and 1 year. The registry protocol was approved by each participating center's research ethics committee or institutional review board (IRB): Directorate of research and studies, Ministry of Health - Sultanate of Oman; King Saud University's IRB, Kingdom of Saudi Arabia; Sheikh Khalifa medical city's IRB, UAE; Hamad Medical Corporation's IRB, Qatar; Mohammed Bin khalifa cardiac center's IRB, Bahrain; Sana'a University' IRB, Yemen and Ministry of health's IRB in Kuwait .The study was registered at clinicaltrials.gov with number NCT01467973. A written informed consent was obtained from all patients

Acute HF was further classified as either acute decompensated chronic heart failure (ADCHF) or acute de-novo heart failure (ADNHF). ADCHF was defined as worsening of HF in patients with a previous diagnosis or hospitalization for HF. ADNHF was defined as acute HF in patients with no prior history of heart failure. All patients were followed-up at 3 months by telephone, and at 1 year either by telephone or by a clinic visit. The registry data was collected on-line using a dedicated Web-site including demographics, risk factors, medical history, clinical manifestations, investigations, medications with dose and management. The participating hospitals ranged from secondary care hospitals to tertiary care hospitals with interventional facilities including device therapy.

The inclusion criteria for this analysis was those patients who were on beta-blockers at time of admission and had a left ventricular ejection fraction (LVEF) < 40%. Those patients with preserved left ventricular function and not on beta-blockers at time of admission were excluded from further analysis. Furthermore, 2 cohorts were created, the first with ADCHF and the second with ADNHF. The main outcome measures were mortality, re-hospitalization for HF, and length of hospital stay. A scheme of the current prospective trial is described in figure 1.

Baseline categorical variables and outcome measures were summarized using frequency distributions whiles means and standard deviations were used for continuous variables. Outcome measures and baseline patients' characteristics were compared between the two groups: withdrawal and non-withdrawal of beta-blockers using the Chi-squared test (or Fisher's exact test when expected cell counts fell below 5) for categorical variables and the student's t test or Wilcoxon rank sum test for numeric variables. Multivariate logistic regression analysis performed for in-hospital and 3-months included variables that were significantly different between the two groups in addition to age and gender. The model included age, gender, non-compliance to medication, systolic blood pressure (SBP), diastolic blood pressure (DBP), left ventricular ejection fraction (LVEF), creatinine, aspirin, statins and inotropes for ADCHF; and age, gender, ACE-inhibitors and inotrops for ADNHF. Adjusted Odds Ratios (OR) and 95% Confidence intervals with p values are presented. All analyses were done separately for the ADCHF and ADNHF patients. In addition, several sensitivity analyses were performed. Propensity scores were computed using logistic regression with membership in the two groups as the outcome and baseline variables that were significantly different between the groups as the independent variables. These scores were used to adjust the association between the mortality outcomes and the main variable (membership in each group) using multivariate logistic regression. Moreover, propensity score matching using the most influential variable (inotropes) was used and the main comparison between the two groups was assessed with and without adjustment to variables that

were still significantly different between the two groups even after matching. In ADCHF, variables adjusted after propensity score matching were gender, non-compliance to medication, SBP, DBP, statins and aspirin whereas in ADNHF we only adjusted for ACE-inhibitors as the sample sizes became small after matching. Statistical significance was set at the 5% level (two-tailed test). All analyses were done using IBM-SPSS version 23.0.

Results:

Out of the total 5005 participants in the GULF-CARE, 2208 (44.1%) patients were already on beta-blockers on inclusion. Further, beta-blockers were prescribed in 1278 (42.2%) patients with a LVEF <40%. Among those, 1018 (79.9%) were diagnosed with acute decompensated chronic HF (ADCHF) and 260 (20.4%) with acute do-novo heart failure (ADNHF). As shown in table 1, Patients with ADCHF tended to have more comorbidities than patients with ADNHF. They had a higher prevalence of coronary artery disease (CAD), chronic kidney disease (CKD), valvular heart disease, atrial fibrillation (AF) and a lower LVEF; which could explain the more common use of angiotensin receptor antagonists (ARBs), aldosterone antagonists, vitamin K antagonists (VKA) and diuretics in these patients. Interestingly, they smoked less, a phenomenon that could be due to the effect of earlier life-style changes and anti-smoking campaigns in patients with CHF.

Table 1: Baseline characteristics of patients on beta-blockers on admission and a left ventricular ejection fraction <40% included in the Gulf-Care.

	All patients in Gulf Care N=5005	**Patients with a LVEF <40% on beta-blockers on admission N=1278**		**P value ***
		Patients with ADCHF and a LVEF <40%, on beta-blockers on admission.	**Patients with ADNHF and a LVEF<40%, on beta-blockers on**	

		N=1018	admission. N=260	
Age (years)	59±15	61.0±13.9	59.8±13.8	0.21
Male gender	3131(62.6%)	751(73.8%)	177(68.1%)	0.07
BMI (kg/m^2)	28±6	27.7±5.8	28.1±5.7	0.26
Hypertension	3059(61.1%)	673(66.1%)	181(69.6%)	0.29
Diabetes Mellitus	2492(49.8%)	569(55.9%)	147(56.5%)	0.86
Hyperlipidemia	1799(35.9%)	464(45.6%)	106(40.8%)	0.16
Smoking	1103(22%)	162(15.9%)	67 (25.8%)	0.001
Race				
Arabs	4516(90.2%)	937 (92.0%)	232(89.2%)	0.04
Asians	473(9.5%)	77(7.6%)	28(10.8%)	
Others	16(0.3%)	4(0.4%)	-	
Past – medical history				
Known CAD	2337(46.7%)	676(66.4%)	150(57.7%)	0.008
Stroke /TIAs	404(8%)	96(9.4%)	29(11.2%)	0.40
Valvular heart disease	675(13.5%)	154(15.1%)	19(7.3%)	0.001
Atrial fibrillation	607(12%)	170(16.7%)	23(8.8 %)	0.001
CKD	744(14.9%)	215(21.1%)	28(10.8%)	0.001
Etiology				
Non-compliance to medication	964(19%)	300(29.5%)	40(15.4%)	0.05
IHD	1365(27%)	204(20,0%)	117(45.0%)	0.67
HTN	410(8.2%)	46(4.5%)	12(4.6%)	0.26
Arrhythmia	301(6%)	61(6.0%)	11(4.2%)	0.49
Anemia	143(3.1%)	23(2.3%)	5(1.9%)	0.50
Renal failure	221(4.4%)	58(5.7%)	9(3.5%)	0.19
Clinical and biochemical parameters				

HR, b.p.m	77.6±12.8	94.4±22.4	94.6±22.3	0.92
SBP, mmHg	118±18	126.6±30.6	133.6±32.4	0.002
DBP, mmHg	70±12	76.4±17.9	80.5±19.3	0.001
LVEF (%)	36.9±14	26.6±7.1	28.8±7.2	0.001
BNP, pg/mL	5324±4523	6847±9679	5227±4924	0.21
Creatinine, mmol/L	130±116	137.7±116.3	128.5±121.9	0.24
Medications				
Carvedilol	1099(21.9%)	649(63.8%)	100 (38.5%)	0.001
Bisoprolol	626 (12.5%)	286 (28.1%)	90 (34.6%)	0.04
Metoprolol	299 (5.9%)	64 (6.3%)	35 (13.5%)	0.001
Atenolol	184 (3.6%)	19 (1.9%)	35 (13.5%)	0.001
ACE-inhibitors	2762(55.2%)	652(64.0%)	166(63.8%)	0.96
ARBs	645(12.9%)	180(17.7%)	23(8.8%)	0.001
Statins	2555(51%)	751 (73.8%)	180(69.2%)	0.14
Aspirin	3089(61.7%)	832 (81.7%)	204(78.5%)	0.23
VKA	618(12%)	221(21.7%)	19(7.3%)	0.001
Ibravadine	115(2.3%)	48(4.7%)	7(2.7%)	0.15
Aldosterone antagonists	840(16.8%)	419(41.2%)	45(17.3%)	0.001
Clopidogrel	966(19%)	301(29.6%)	81(31.2%)	0.61
Diuretics	2882(57.6%)	920(90.4%)	113(43.5%)	0.001
Inotropes use during hospitalization	783 (16%)	156 (15.3%)	51 (19.6%)	0.96

All values are given as n (%) or mean ±SD. * p value: patients with acute decompensated chronic heart failure and LVEF <40% on beta-blockers on admission vs. de – Novo heart failure and LVEF <40% on beta-blockers on admission. ADCHF = Acute decompensated chronic heart failure, ADNHF = Acute de-novo heart failure, BMI=body mass index, CAD= coronary artery disease, TIAs=transient ischemic attacks, CKD=chronic kidney disease, HR=heart rate, SBP= systolic blood pressure, DBP= diastolic blood pressure, LVEF = Left ventricular ejection fraction, VKA= Vitamin K antagonists, ARBs= Angiotensin receptor blockers.

Beta-blockers were withdrawn in 9% of the patients in the ADCHF group and 13.8% in the ADNHF group. Those ADCHF patients in whom beta-blockers were discontinued had a lower blood pressure at inclusion and half of them required inotropic support during hospitalization **(supplementary table 1).** ADNHF patients who continued beta-blockade therapy were more commonly prescribed ACE-inhibitors and required less inotropic support **(supplementary table 2).**

In the ADCHF group, 15 (1.6%) in-hospital deaths occurred in patients whose beta-blocker therapy was not withdrawn as compared to 37 (40.2%) when beta-blockers were discontinued (p<0.001) (**Table 2**).

Table 2: Effect of non-withdrawal of beta-blockers in acute decompensated chronic heart failure with beta-blocker therapy on admission and a LVEF <40%

	All patients with acute decompensated heart failure, LVEF <40% and on beta-treatment on admission **N=1018**	**Beta-blockers maintained during hospitalization** **N=926(91%)**	**Beta-blockers withdrawn during hospitalization** **N=92(9.0%)**	**P value**
In–hospital outcome				
Death	52/1018(5.1%)	15/926(1.6%)	37/92(40.2%)	<0.001
Length of stay (days)	9.9±15.0	9.7±15.1	12.3±13.6	0.1
3-month follow-up				
Death	86/946(9.1%)	77/896(8.6%)	9/50(18.0%)	0.038
Re-hospitalization for HF	219/859(25.5%)	204/818(24.9%)	15/41(36.6%)	0.09
Length of stay (days)	8.1±7.6	8.1±7.8	7.7±4.3	0.86
12-month follow-up				
Death	139/880(15.8%)	128/835(15.3%)	11/45(24.4%)	0.10

Re-hospitalization for HF	333/741 (44.9%)	316/707 (44.7%)	17/34 (50.0%)	0.54
Length of stay (days)	9.6±12.0	9.6±12.1	10.9±11.1	0.73

The frequencies and percentages for death, re-hospitalization for heart failure (HF) and length of hospital stay. Death rates were cumulative. All values are given as n (%) or mean ±SD.

Multivariate analysis showed that age, gender, non-compliance to medication, SBP, DBP, creatinine and statins were not predictors of in-hospital mortality in case of non-withdrawal of beta-blockers. As expected, inotropic use was significantly associated with higher mortality in our model **(Table 3).**

Table 3: Multivariate analysis for intra-hospital and 3-month mortality in patients with ADCHF, a LVEF <40% and beta-blockers on admission.

	Variable	**OR**	**95% .C.I**	**P value**
In-hospital mortality	Age	1.022	0.991-1.055	0.17
	Gender	1.058	0.428-2.618	0.90
	Non-compliance to medication	1.736	0.642-4.698	0.27
	SBP	0.990	0.968-1.014	0.41
	DBP	1.003	0.964-1.044	0.87
	LVEF	1.053	0.998-1.003	0.07
	Creatinine	1.001	0.998-1.001	0.59
	Aspirin	1.357	0.477-3.865	0.56
	Statins	2.083	0.763-5.684	0.15
	Inotropes	20.368	8.241-50.337	<0.001
	Beta-blockers on discharge			
	Beta-blockers withdrawn (reference group)	1	-	

	Beta-blockers maintained	0.050	0.022-0.112	<0.001

3-month mortality	Age	1.029	1.010-1.048	0.002
	Gender	0.974	0.579-1.638	0.92
	Non-compliance to medication	1.267	0.753-2.133	0.37
	SBP	0.993	0.980-1.005	0.26
	DBP	1.005	0.984-1.026	0.66
	LVEF	1.003	0.970-1.037	0.87
	Creatinine	1.001	1.000-1.003	0.15
	Aspirin	1.516	0.828-2.777	0.17
	Statins	1.307	0.747-2.284	0.34
	Inotropes	1.456	0.759-2.793	0.25
	Beta-blockers on discharge			
	Beta-blockers withdrawn (reference group)	1		
	Beta-blockers maintained	0.513	0.231-1.143	0.10

SBP= systolic blood pressure, DBP = diastolic blood pressure, LVEF = Left ventricular ejection fraction.

Nevertheless, non-withdrawal of beta-blockers was associated with less mortality risk even after correcting for all the parameters (OR=0.05, 95% CI: 0.022-0.112, p<0.001). To confirm our findings, we performed a propensity score matching on inotropic use **(supplementary Table 3).** Non-withdrawal of beta-blockers was associated with less mortality in the propensity model (OR=0.05, 95% CI: 0.015-0.170, p<0.001), even after correcting for variables that remained significantly different in the new model (OR=0.084, 95% CI: 0.015-0.468, p=0.005). At 3 months, fewer deaths also occurred in the group of patients whose beta-blockers therapy was not withdrawn (p= 0.038). However, after multivariate logistic regression analysis, the protection conferred by beta-blockade continuation was lost (OR=0.513, 95% CI: 0.231-1.143, p=0.10).

In the ADNHF group, 5 (2.2%) in-hospital deaths occurred in patients whose beta-blocker therapy was not withdrawn as compared to 17 (47.2%) when beta-blockers were discontinued (p<0.001). However, mortality rates were comparable at 3 months and one year **(Table 4).**

Table 4: Effect of non-withdrawal of beta-blockers in acute decompensated de-novo heart failure with beta-blocker therapy on admission, and a LVEF <40%

	All patients with de-novo heart failure, LVEF <40% and on beta-blockers treatment on admission. **N=260**	**Beta-blockers maintained during hospitalization** **N=224(86.2%)**	**Beta-blockers withdrawn during hospitalization** **N=36(13.8%)**	**p- value**
In–hospital outcome				
Death	22/260(8.5%)	5/224(2.2%)	17/36(47.2%)	<0.001*
Length of stay (days)	9.7±16.1	9.6±16.6	10.1±12.1	0.86
3 months follow-up				
Death	9/232(3.9%)	7/214(3.3%)	2/18(11.1%)	0.14
Re-hospitalization for HF	39/223(17.5%)	38/207(18.4%)	1/16(6.3%)	0.31
Length of stay (days)	8.8±9.8	8.8±9.9	8.0±NE	NE
1 year follow-up				
Death	15/221(6.8%)	13/206(6.3%)	2/15(13.3%)	0.27
Re-hospitalization for HF	61/206(29.6%)	73/193(37.8%)	3/13(23.1%)	0.38

Length of stay (days)	7.9±7.5	8.2±7.6	2.7±2.1	0.21

The frequencies and percentages for death, re-hospitalization for heart failure (HF) and length of hospital stay. Death rates were cumulative. All values are given as n (%) or mean ±SD. NE=not estimable.

Multivariate analysis did not show that age, gender or Ace-inhibitors, which were different among both groups, predicted mortality **(Table 5).**

Table 5: Multivariate analysis for intra-hospital death in patients with ADNHF, a LVEF <40% and beta-blockers on admission

Variable	OR	95 % C.I	P value
Age	1.047	0.992-1.105	0.097
Gender	2.179	0.431-10.989	0.346
ACE-inhibitors	1.112	0.215-5.757	0.899
Inotrops	172.272	16.002-1854.600	<0.001*
Beta-blockers			
Beta-blockers withdrawn (reference group)	1		
Beta-blockers maintained	0.018	0.003-0.122	<0.001*

SBP= systolic blood pressure, DBP = diastolic blood pressure, LVEF = Left ventricular ejection fraction.

Similarly, to the ADCHF, inotropic use was highly associated with mortality. We also performed a propensity score matching on inotropic use **(supplementary Table 4)** and confirmed that beta-blocker continuation in ADNHF has a favorable outcome (OR=0.05, 95% CI: 0.015-0.170, p<0.001), even after

correcting for variables that remained significantly different between both groups in the new model (OR=0.047, 95% CI: 0.013-0.169, p<0.001). Similarly to patients with ADCHF, re-hospitalization for HF and length of hospital stay were unaffected by the withdrawal of beta-blockers.

Discussion

This observational study demonstrates that pursuing beta-blocker therapy during acute HF confers to patients with chronic and de-novo acute HF cardiovascular protection and decreases mortality. Interestingly, randomized placebo-controlled trials that assessed pursuing beta-blockers versus withdrawal during acute HF are missing; available data are extrapolated from post-hoc analysis. The B-convinced was designed as a non-inferiority trial and demonstrated only safety of beta-blockers during acute decompensation[9]. In a retrospective analysis of the SURVIVE study that initially assessed 2 inotropic treatments in critical patients with acute HF, the benefit associated with non-withdrawal of beta-blockers was lost after correcting for HF covariates; only patients who never received beta-blockers had a worse outcome as compared to patients who were on these drugs at inclusion and on discharge[10]. In a sub-analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization (ESCAPE) that assessed pulmonary artery catheter use among patients admitted with acute HF, patients already prescribed beta-blockers on admission had a lower 6-month mortality risk and a shorter hospitalization stay[13]. Outcomes of the Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF), designed as a randomized placebo-controlled trial, failed to test the superiority of milnirone to placebo in patients with ADCHF[14]. Further observational analysis showed that withdrawal of beta-blockers was associated with a greater risk of 2-month mortality and re-hospitalization for HF despite limitations due to the use of milnirone in those patients and the small number of patients analyzed[15].

Our results are comparable to previous observational studies from North America and Europe. In the Italian Survey on Acute Heart Failure, withdrawal of beta-blockers during acute HF was associated with almost 4-fold increase in the risk of intra-hospital mortality[16]. The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) is one of the largest Northern American registries of patients admitted with acute HF. Maintenance of beta-blockers during

acute decompensation was associated with better outcome in post-discharge mortality[17]. Consistent with our findings, Prins et al reported in a recent meta-analysis that included over 2700 patients treated with beta-blockers and hospitalized for acute HF, that withdrawal of beta-blockers significantly increased in-hospital and short term mortality, and re-hospitalization for HF [18].

Despite firm safety data and un-doubted long-term benefit, beta-blocker therapy remains under-prescribed. In our study, only 44.1% of all patients presenting with acute HF and 44.2 % of patients with a LVEF<40% were treated with beta-blockers. The frequency of beta-blockers prescription is variable according to cohorts and ranges from 32% in the "Italian Survey on Acute Heart Failure" study [16] to 53.3% in the SURVIVE study[10] and 62% in the ESCAPE trial [13].

It is not known why withdrawal of beta-blockers in acute HF is associated with a worse prognosis. Activation of the sympathetic system, increase of catecholamine levels and alterations in cardiac β-receptors are the hallmark of chronic HF; therefore beta-blocker therapy in chronic HF could limit the deleterious effect of chronic β-receptor stimulation such as arrhythmias, hypertrophy and cardiomyocytes apoptosis[19]. It may be possible that withdrawal of beta-blockers in the acute phase takes away earlier protective effect of beta-adrenergic inhibition at a time when the neuro-hormonal system is activated and catecholamines are significantly increased[20].

Managing beta-blockers during acute HF is still unclear to most physicians. The Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial investigators were the first to report that in-hospital initiation of beta-blockers was safe compared to post-discharge[21]. The latest guidelines from both the Society of Cardiology (ESC)[22] and the American college of Cardiology foundation (ACCF)/American heart association (AHA) [23] recommend initiating a beta-blocker therapy following acute HF as soon as the patient is stable and before discharge. However, uncertainty persists in regards to continuing beta-blockers during an acute decompensation. Beta-blockade therapy discontinuation during AHF is variable. In older studies such as the OPTIME-CHF, beta-blockers were

withdrawn in over 20% of patients [15]. In our study, beta-blockers were withdrawn in 9% of patients with ADCHF and 13.8% of patients with ADNHF. Those numbers are almost similar to the Italian Survey on Acute Heart Failure in which Orso et al reported a withdrawal rate of 9% in all AHF patients with beta-blockers on admission [16] However, Bohm et al reported a lower rate (6.8%) in the retrospective analysis of the SURVIVE study[10].

It is not known why mortality risk reduction extends up to 3 months in ADCHF but not in ADNHF although the first group has higher cardiovascular comorbidities and more severe risk factors. One explanation could be the higher prescription of cardioprotective drugs such as ACE inhibitors, ARBs, diuretics; all having shown to reduce mortality in patients with chronic HF and improve the outcome [24-26]. One other explanation would also be the frequent use of beta-blockers approved for HF in patients with ADCHF whereas the prescription of non-HF selective beta-blockers such as atenolol was more common in ADNHF. Finally, we cannot rule out that the relatively small number of patients with ADNHF, coupled to an even smaller death rate at 3 months, does not enable us draw any meaningful conclusions on long-term mortality in those patients.

Our study has a few limitations. Like any observational study, selection bias could exist. The decision of beta-blocker withdrawal during acute HF could have been to different factors not accounted for in our analysis such as their side effects. Above all, beta-blocker therapy could have been withdrawn in the more severe patients with a poor prognosis. Despite the correction on available cofounding factors, we could have missed other markers of disease severity that were not recorded in the cohort. In addition, we could not determine whether the dosage of beta-blockers on admission, or any reduction during hospitalization, might have influenced the outcome. Finally, the duration of beta-blocker treatment prior to acute HF was not recorded; this variable could also be a confounding factor since long-term beta-blocker treatment could have been more beneficial than short-term.

Conclusion

Our study suggests non-withdrawal of beta-blocker therapy during acute heart failure reduces intra-hospital mortality risk in patients with acute decompensated chronic and de-novo heart failure, but does influence 3- and 12- mortality, re-hospitalization for heart failure, and the length of hospital stay. Our findings could only be validated in randomized controlled trials designed to show the superiority of non-withdrawal of beta-blockade therapy and also determine whether beta-blocker dose should be reduced or kept unchanged compared to a withdrawal strategy.

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Footnotes

Contribution: KS, KFA, NA, AA-A, MA-J, BB, WA, MR, NB, HA, AA-M, HAF, AE, PP and JAS were involved in the design of the Gulf CARE registry and patient enrolment and ensuring quality control of the study. CAK designed the analysis and wrote the manuscript. ZM and RS carried out the statistical analyses. All authors approved the final version of the manuscript.

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Competing interests: None.

Data sharing statement: The data includes human data. To protect participant privacy, the data is available on request from the corresponding author:

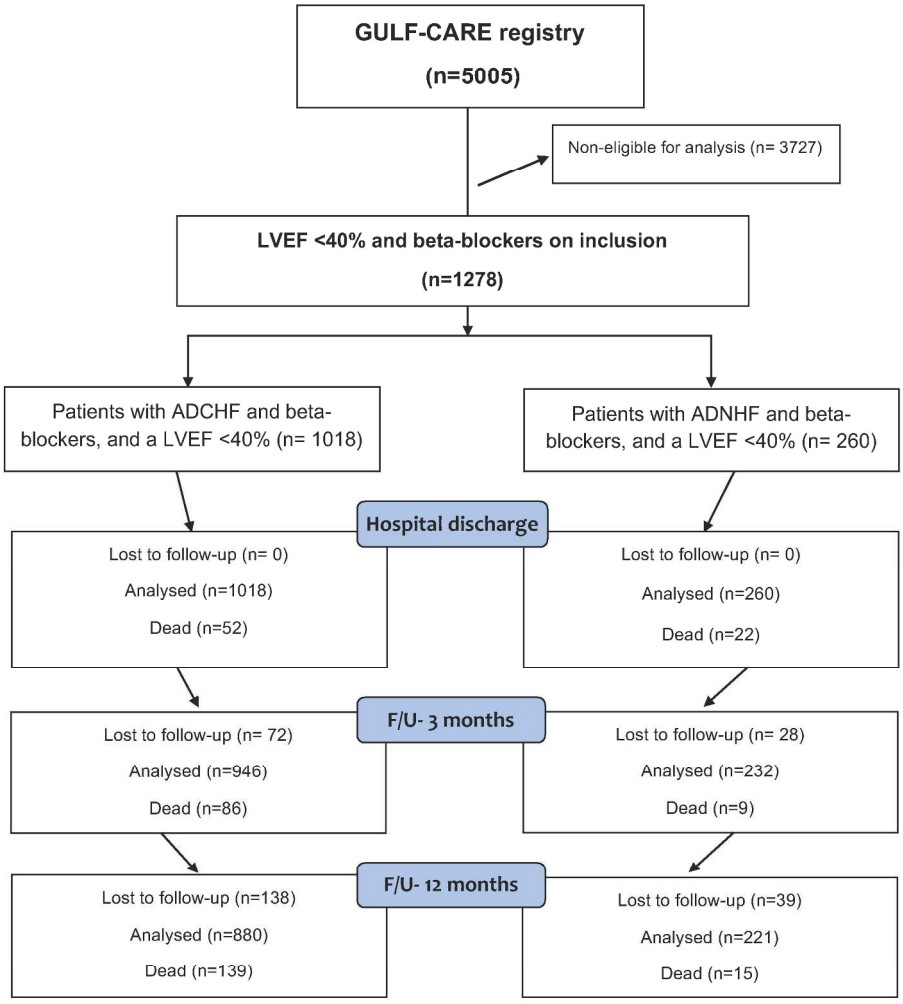

Figure 1: Flow chart of the current prospective analysis. 1278 patients with a LVEF <40% and beta-blockers on admission were analyzed from the 5005 participants in the GULF-CARE registry. ADCHF = Acute decompensated chronic heart failure, ADNHF = Acute de-novo heart failure, LVEF = Left ventricular ejection fraction, F/U= Follow-up.

211x230mm (300 x 300 DPI)

Supplementary table 1: Baseline characteristics of patients with acute decompensated chronic heart failure and a left ventricular ejection fraction <40%, on beta-blockers on admission

	Patients with ADCHF with a LVEF <40% and beta-blockers on admission N=1018	**Beta-blockers maintained during hospitalization N=926**	**Beta-blockers withdrawn during hospitalization N=92**	**p value**
Age (years)	61.0±13.9	61.1±13.7	60.3±15.8	0.64
Male gender	751(73.8%)	689(74.4%)	62(67.4%)	0.14
BMI (kg/m^2)	27.7±5.8	27.6±5.8	28.3±5.7	0.28
Hypertension	673(66.1%)	620(67.0%)	53(57.6%)	0.07
Diabetes Mellitus	569(55.9%)	518(55.9%)	51(55.4%)	0.92
Hyperlipidemia	464(45.6%)	419(45.2%)	45(48.9%)	0.50
Smoking	162(15.9%)	149(16.1%)	13(14.1%)	0.62
Race				
Arabs	937 (92.0%)	852(92.0%)	85(92.4%)	0.37
Asians	77(7.6%)	71(7.7%)	6(6.5%)	
Others	4(0.4%)	3(0.3%)	1(1.1%)	
Past – medical history				
Known CAD	676(66.4%)	617(66.6%)	59(64.1%)	0.62
Stroke /TIAs	96(9.4%)	89(9.6%)	7(7.6%)	0.53
Valvular heart disease	154(15.1%)	139(15.0%)	15(16.3%)	0.74
Atrial fibrillation	170(16.7%)	157(17.0%)	13(14.1%)	0.48
CKD	215(21.1%)	192(20.7%)	23(25.0%)	0.33
Etiology				
Non-Compliance Medication	300(29.5%)	281(30.3%)	19(20.7%)	0.052
IHD	204(20,0%)	184(19.9%)	20(21.7%)	0.66
HTN	46(4.5%)	44(4.8%)	2(2.2%)	0.42
Arrhythmia	61(6.0%)	57(6.2%)	4(4.3%)	0.48
Anemia	23(2.3%)	20(2.2%)	3(3.3%)	0.45
Renal failure	58(5.7%)	50(5.4%)	8(8.7%)	0.19
Clinical and biochemical parameters				

HR, b.p.m	94.4±22.4	94.8±22.5	91.1±21.2	0.14
SBP, mmHg	126.6±30.6	127.8±30.3	114.2±31.3	<0.001
DBP, mmHg	76.4±17.9	77.2±17.8	67.8±17.2	<0.001
LVEF (%)	26.6±7.1	26.7±7.1	25.6±7.6	0.16
BNP, pg/mL	6847±9679	6851±9831	6777±7271	0.97
Creatinin, mmol/L	137.7±116.3	135.7±113.4	158.5±141.4	0.07
Medications				
Carvedilol	649(63.8%)	589 (63.6%)	60(65.2%)	0.75
Bisoprolol	286 (28.1%)	265(28.6%)	21(22.8%)	0.23
Metoprolol	64 (6.3%)	57(6.2%)	7(7.6%)	0.58
Atenolol	19 (1.9%)	15(1.6%)	4(4.3%)	0.08
ACE-inhibitors	652(64.0%)	600(64.8%)	52(56.5%)	0.11
ARBs	180(17.7%)	167 (18.0%)	13(14.1%)	0.34
Statins	751 (73.8%)	694(74.9%)	57(62.0%)	0.007
Aspirin	832 (81.7%)	768(82.9%)	64(69.6%)	0.002
VKA	221(21.7%)	196 (21.2%)	25(27.2%)	0.18
Ibravadine	48(4.7%)	42 (4.5%)	6(6.5%)	0.43
Aldosterone antagonists	419(41.2%)	383 (41.4%)	36 (39.1%)	0.67
Clopidogrel	301(29.6%)	274 (29.6%)	27(29.3%)	0.96
Diuretics	920(90.4%)	835(90.2%)	85(92.4%)	0.49
Inotrops use during hospitalization	156 (15.3%)	110 (11.9%)	46 (50.0%)	<0.001*

All values are given as n (%) or mean ±SD. ADCHF = Acute decompensated chronic heart failure, BMI=body mass index, CAD= coronary artery disease, TIAs=transient ischemic attacks, CKD=chronic kidney disease, HR=heart rate, SBP= systolic blood pressure, DBP= diastolic blood pressure, LVEF = Left ventricular ejection fraction, VKA= Vitamin K antagonists, ARBs= Angiotensin receptor blockers.

Supplementary table 2: Baseline characteristics of patients with acute de-novo heart failure and a left ventricular ejection fraction <40%, on beta-Blockers on admission.

	Patients with ADCHF with a LVEF <40% and beta-blockers on admission N=260	**Beta-blockers maintained during hospitalization N=224**	**Beta-blockers withdrawn during hospitalization N=36**	**p**
Age (years)	59.8±13.8	60.1±13.8	57.9±13.9	0.35
Male gender	177(68.1%)	151(67.4%)	26(72.2%)	0.56
BMI (kg/m^2)	28.1±5.7	28.1±5.8	28.1±5.2	0.99
Hypertension	181(69.6%)	158(70.5%)	23(63.9%)	0.42
Diabetes Mellitus	147(56.5%)	123(54.9%)	24(66.7%)	0.18
Hyperlipidemia	106(40.8%)	92(41.1%)	14(38.9%)	0.80
Smoking	67 (25.8%)	60(26.8%)	7(19.4%)	0.35
Race				
Arabs	232(89.2%)	201 (89.7%)	31(86.1%)	0.56
Asians	28(10.8%)	23(10.3%)	5(13.9%)	
Others	-	-	-	
Past – medical history				
Known CAD	150(57.7%)	130(58.0%)	20(55.6%)	0.78
Stroke /TIAs	29(11.2%)	24(10.7%)	5(13.9%)	0.57
Valvular heart disease	19(7.3%)	16(7.1%)	3 (8.3%)	0.73
Atrial fibrillation	23(8.8 %)	19(8.5%)	4(11.1%)	0.53
CKD	28(10.8%)	22(9.8%)	6 (16.7%)	0.24
Etiology				
Non-Compliance Medication	40(15.4%)	37(16.5%)	3(8.3%)	0.20
IHD	117(45.0%)	100(44.6%)	17(47.2%)	0.77
HTN	12(4.6%)	11(4.9%)	1(2.8%)	0.99
Arrhythmia	11(4.2%)	8(3.6%)	3(8.3%)	0.18
Anemia	5(1.9%)	5(2.2%)	0(0.0%)	0.99
Renal failure	9(3.5%)	8(3.6%)	1(2.8%)	0.99
Clinical and biochemical				

parameters				
HR, b.p.m	94.6±22.3	94.6±21.2	94.7±28.7	0.99
SBP, mmHg	133.6±32.4	134.6±31.9	126.8±35.0	0.19
DBP, mmHg	80.5±19.3	81.0±18.8	77.6±22.4	0.34
LVEF (%)	28.8±7.2	29.0±7.2	27.5±7.4	0.23
BNP, pg/mL	5227±4924	5361±5046	3883±1614	0.52
Creatinin, mmol/L	128.5±121.9	124.9±123.5	151.1±110.2	0.23
Medications				
Carvedilol	100 (38.5%)	84(37.5%)	16(44.4%)	0.42
Bisoprolol	90 (34.6%)	82(36.6%)	8(22.2%)	0.09
Metoprolol	35 (13.5%)	25 (11.2%)	10(27.8%)	0.01
Atenolol	35 (13.5%)	33 (14.7%)	2(5.6%)	0.18
ACE-inhibitors	166(63.8%)	150(67.0%)	16(44.4%)	0.009
ARBs	23(8.8%)	18(8.0%)	5(13.9%)	0.33
Statins	180(69.2%)	154(68.8%)	26(72.2%)	0.67
Aspirin	204(78.5%)	176(78.6%)	28(77.8%)	0.91
VKA	19(7.3%)	16(7.1%)	3(8.3%)	0.73
Ibravadine	7(2.7%)	7(3.1%)	0(0.0%)	0.59
Aldosterone antagonists	45(17.3%)	38(17.0%)	7(19.4%)	0.71
Clopidogrel	81(31.2%)	69(30.8%)	12(33.3%)	0.76
Diuretics	113(43.5%)	98(43.8%)	15(41.7%)	0.81
Inotrops use during hospitalization	51 (19.6%)	32 (14.3%)	19 (52.8%)	<0.001

All values are given as n (%) or mean ±SD. ADNHF = Acute de-novo heart failure, BMI=body mass index, CAD= coronary artery disease, TIAs=transient ischemic attacks, CKD=chronic kidney disease, HR=heart rate, SBP= systolic blood pressure, DBP= diastolic blood pressure, LVEF = Left ventricular ejection fraction, VKA= Vitamin K antagonists, ARBs= Angiotensin receptor blockers.

Supplementary table 3: Variables after propensity score matching on inotrops in patients with acute decompensated chronic heart failure, a left ventricular ejection fraction <40% and on beta-blockers on admission.

	Beta-blockers continued N=92	**Beta-blockers withdrawn N=92**	**p value**
Age (years)	60.3±12.7	60.3±15.8	0.98
Male gender	74 (80.4%)	62(67.4%)	0.044*
Noncompliance with medication	51 (55.4%)	19 (20.7%)	<0.001*
SBP, mmHg	147.5±39.8	114.2±31.3	<0.001*
DBP, mmHg	95.9±23.4	67.8±17.2	<0.001*
LVEF (%)	28.3±6.7	25.6±7.6	0.011*
Creatinine, mmol/L	126.7±103.4	158.5±141.4	0.08
Statins	79 (85.9%)	57(62.0%)	<0.001*
Aspirin	92 (100.0%)	64(69.6%)	<0.001*
Inotrops	46 (50.0%)	46 (50.0%)	1.000

All values are given as n (%) or mean ±SD. SBP= systolic blood pressure, DBP= diastolic blood pressure, LVEF = Left ventricular ejection fraction.

Supplementary table 4: Variables after propensity score matching on inotrops in patients with acute de-novo heart failure, a left ventricular ejection fraction LVEF <40% and on beta-blockers on admission.

	Beta-blockers continued N=36	**Beta-blockers withdrawn n=36**	**p value**
Age	59.9±12.7	57.9±13.9	0.514
Male Gender	11 (30.6%)	10 (27.8%)	0.795
ACE-inhibitors	25 (69.4%)	16 (44.4%)	0.032*
Inotrops	19 (52.8%)	19 (52.8%)	1.000

All values are given as n (%) or mean ±SD.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract- done page 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found- done page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported- done page 4
Objectives	3	State specific objectives, including any prespecified hypotheses- done page 4
Methods		
Study design	4	Present key elements of study design early in the paper- done page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection- done page 5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up- done page 5 *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls- not applicable *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants. not applicable
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed, not applicable *Case-control study*—For matched studies, give matching criteria and the number of controls per case- not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable-done page 5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group-done page 5
Bias	9	Describe any efforts to address potential sources of bias-done page 6
Study size	10	Explain how the study size was arrived at-done page 5 to 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why-done page 6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding- done page 6
		(*b*) Describe any methods used to examine subgroups and interactions-done page 6
		(*c*) Explain how missing data were addressed-done page 6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed- done page 7 *Case-control study*—If applicable, explain how matching of cases and controls was addressed not applicable *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy not applicable
		(*e*) Describe any sensitivity analyses-done page 6

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed- page 6
		(b) Give reasons for non-participation at each stage- page 6-7
		(c) Consider use of a flow diagram- not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders- done page 6-7 and table 1
		(b) Indicate number of participants with missing data for each variable of interest- done page 6-7
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)- done page 7-8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time- done table 2 and 4
		Case-control study—Report numbers in each exposure category, or summary measures of exposure-not applicable.
		Cross-sectional study—Report numbers of outcome events or summary measures-not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included- done page 6 to 8
		(*b*) Report category boundaries when continuous variables were categorized- done page 6 to 8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses- done page 7-8
Discussion		
Key results	18	Summarise key results with reference to study objectives- done page 8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias - done page 10.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence- done pages from 8 to 10
Generalisability	21	Discuss the generalisability (external validity) of the study results-done page 10
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based- done page 13.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.