Observational Study

Medicine

OPEN

Outcomes of guideline-based medical therapy in patients with acute heart failure and reduced left ventricular ejection fraction

Observations from the Gulf acute heart failure registry (Gulf CARE)

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Abstract

This study aimed to report on the use, predictors and outcomes of guideline-based medical therapy (GBMT) in patients with acute heart failure (HF) with reduced ejection fraction of <40% (HFrEF), from seven countries in the Arabian Gulf.

Patients with acute HFrEF (N = 2680), aged 18 years or older, and hospitalized February–November 2012 were recruited and data were collected post discharge at 3 months (n = 2477) and 1 year (n = 2418). The use and doses of GBMT were evaluated as per European, American and Canadian HF guidelines. Analyses were performed using multivariate logistic regression. This study was registered at clinicaltrials.gov (NCT01467973).

The majority of patients were on dual (39%) and triple (39%) GBMT modalities, 14% received one GBMT medication, while 7.2% were not on any GBMT medications. On admission, 80% of patients were on renin-angiotensin system (RAS) blockers, 75% on b-blockers and 56% on mineralocorticoid receptor antagonists (MRAs), with a small proportion of these patients were taking target doses (RAS blockers 13%, b-blockers 7.3%, MRAs 14%). Patients taking triple GBMT were younger ($P < .001$), less likely to have comorbidities such as diabetes mellitus ($P < .001$) and CKD/dialysis ($P < .001$), less likely to receive in-hospital invasive treatments ($P < .001$), and more likely to be treated by a cardiologist ($P < .001$), than patients on a single medication. Patients taking triple GBMT showed significantly reduced all-cause mortality both at 3-months ($P = .048$), and at 12-months ($P = .003$), compared to patients taking no GBMT.

Triple GBMT prescribing and dosing in patients with HFrEF were suboptimal in the Arabian Gulf. Further studies are required to investigate GBMT utilization and dosing in the outpatient setting.

Abbreviations: ACE = angiotensin-converting enzyme, ADCHF = acute decompensated chronic heart failure, AHF = acute heart failure, aOR = adjusted odds ratio, ARB = angiotensin II receptor blockers, BNP = brain natriuretic peptide, BP = blood pressure, CABG = coronary artery bypass graft, CAD = coronary artery disease, CHAMP-HF = CHAnge the Management of Patients with Heart Failure, CI = confidence interval, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary

Gulf CARE is an investigator-initiated study conducted under the auspices of the Gulf Heart Association and supported by Servier, Paris, France. Centres in Saudi Arabia were also supported by the Saudi Heart Association. The sponsors had no role in study design, data collection and analysis, interpretation or publication. However, the current study was not funded.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Jan RK, Alsheikh-Ali A, Mulla AA, Sulaiman K, Panduranga P, Al-Mahmeed W, Bazargani N, Al-Suwaidi J, Al-Jarallah M, Al-Motarreb A, Salam A, Al-Zakwani I. Outcomes of guideline-based medical therapy in patients with acute heart failure and reduced left ventricular ejection fraction: observations from the Gulf acute heart failure registry (Gulf CARE). Medicine 2022;101:23(e29452).

Received: 4 October 2021 / Received in final form: 22 April 2022 / Accepted: 22 April 2022

http://dx.doi.org/10.1097/MD.0000000000029452

disease, CRF = case report form, CRT-D = cardiac resynchronization therapy defibrillator, CRT-P = cardiac resynchronization therapy pacemaker, eGFR = estimated glomerular filtration rate, ESC = European Society of Cardiology, GBMT = guideline-based medical therapy, Gulf CARE = Gulf acute heart failure registry, HF = heart failure, HFrEF = heart failure with reduced ejection fraction; ACC = American College of Cardiology, HR = heart rate, ICD = implantable cardioverter defibrillator, MRAs = mineralocorticoid receptor antagonists, OLS = ordinary least squares, PCI = percutaneous coronary intervention, PPM = permanent pacemaker, RAS = renin-angiotensin system, SBP = systolic blood pressure, SD = standard deviation, TIA = transient ischemic attack, UAE = United Arab Emirates.

Keywords: drug therapy, guideline adherence, heart failure, Middle East, reduced ejection fraction, registry, survival

1. Introduction

Heart failure (HF) is associated with a globally high disease burden due to recurrent and prolonged hospitalizations and increased mortality.[1–3] Several randomized controlled trials[4–6] and international registries[7–12] have contributed to the development of best practice evidence-based guidelines in patients with HF.[13–17] Guideline-based medical therapy (GBMT) has been shown to improve prognosis and survival in patients with HF with reduced ejection fraction (HFrEF) of <40%.[18–25] The mainstays of GBMT, as recommended by the American College of Cardiology (ACC) and European Society of Cardiology (ESC), are renin-angiotensin system (RAS) blockers (angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)), and b-blockers as first-line therapy and mineralocorticoid receptor antagonists (MRAs) as second-line therapy.[26–28] The ACC recommends that patients with HFrEF are treated with the maximally tolerated doses of appropriate GBMT.[26,28] However, there is evidence that many patients with HFrEF do not receive GBMT, and that less than 25% receive suitable target doses of GBMT.[29] The lack of use of GBMT and/or treatment with doses that are less than 50% of the guideline-recommended target doses are associated with increased morbidity.[30,31]

Although several registries and observational studies have been conducted in HF patients from developed countries, there is a paucity of data on the management of HF in the developing world including the Middle East.[32–34] The Gulf acute heart failure registry (Gulf CARE) is the first multicentre prospective observational survey of patients with acute HF in the Gulf Middle East region.[35,36] The Gulf CARE registry enrolled patients with acute HF admitted to various hospitals from seven countries, namely, Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates (UAE), and Yemen.[35,36] The aim of this paper is to report on the use, predictors and outcomes of GBMT in patients with acute HFrEF in the Arabian Gulf.

2. Methods

Gulf CARE is a multinational, multicentre, prospective registry of patients with acute HF admitted to 47 hospitals in seven Middle Eastern Gulf countries.[35,36] The design, methodology, clinical characteristics, management and outcomes of the Gulf CARE registry have been previously described in detail.[35,36] Briefly, patients with acute HF aged 18 years or older, hospitalized between February 14, 2012 and November 13, 2012, and who were eligible to participate in the study were recruited and followed up at 3 months and at 1 year post discharge. Data collected at the point of initial care and during hospitalization included: demographics, HF aetiology, risk and precipitating factors for acute HF, comorbidities, clinical presentation, investigations including troponin and brain natriuretic peptide (BNP), drug history, defibrillator use, and in-hospital outcome. Additionally, mortality data at 3-months and 12-months follow-up were collected.

A total of 5005 patients with acute HF were enrolled (original Gulf CARE cohort). The present analysis includes only the 2680 patients with reduced ejection fraction of <40% (HFrEF) (Fig. 1). Left ventricular ejection fraction was measured during the index hospitalization. Patients were followed up at 3 months by telephone (n = 2477) and at 1 year (n = 2418) either by telephone or at a clinic visit. Data entry was performed online on a secure study website (www.gulfcare.org) using a customized electronic case record form (CRF), whereby each investigator was assigned an individual username and password for data entry. Data collection and validation details of the Gulf CARE registry has already described and published elsewhere.[36] In summary, all the variables in an online case report form (CRF) were defined (including range provided for numerical data) to standardize data entry. To avoid any missing data, most of the variables were made compulsory, so that the CRF could not be saved until all the required data were entered. A data quality control committee performed audits of the collected data in one hospital of each country, chosen at random. At these sites, 100% of CRFs for enrolled patients were monitored for source documentation and accuracy. The study was approved by the locally appointed ethics committees in each of the seven Gulf countries, and written informed consent was obtained from all participants.[35,36] The study also conforms with the principles outlined in the Declaration of Helsinki. The study was also registered at clinicaltrials.gov (NCT01467973).

2.1. Inclusion criteria

Males and females 18 years of age or older, admitted to any of the participating hospitals with the admission diagnosis of acute HF, were included in the registry. Acute HF was defined according to the ESC as rapid onset of symptoms and signs secondary to abnormal cardiac function and included: firstly, symptoms (dyspnoea at rest or on exercise, fatigue, tiredness, and ankle swelling); secondly, signs (tachycardia, tachypnoea, elevated jugular venous pressure, pulmonary rales, pleural effusion, hepatomegaly, and peripheral oedema); and finally, objective evidence of structural or functional abnormality of the heart at rest (third heart sound, murmurs, cardiomegaly, abnormal echocardiogram, and raised BNP concentration).[13] Acute HF was further classified as either acute decompensated chronic HF (ADCHF) or new-onset acute HF (de novo AHF) based on the 2008 ESC guidelines.[13] ADCHF was defined as worsening of HF in patients with a previous diagnosis or

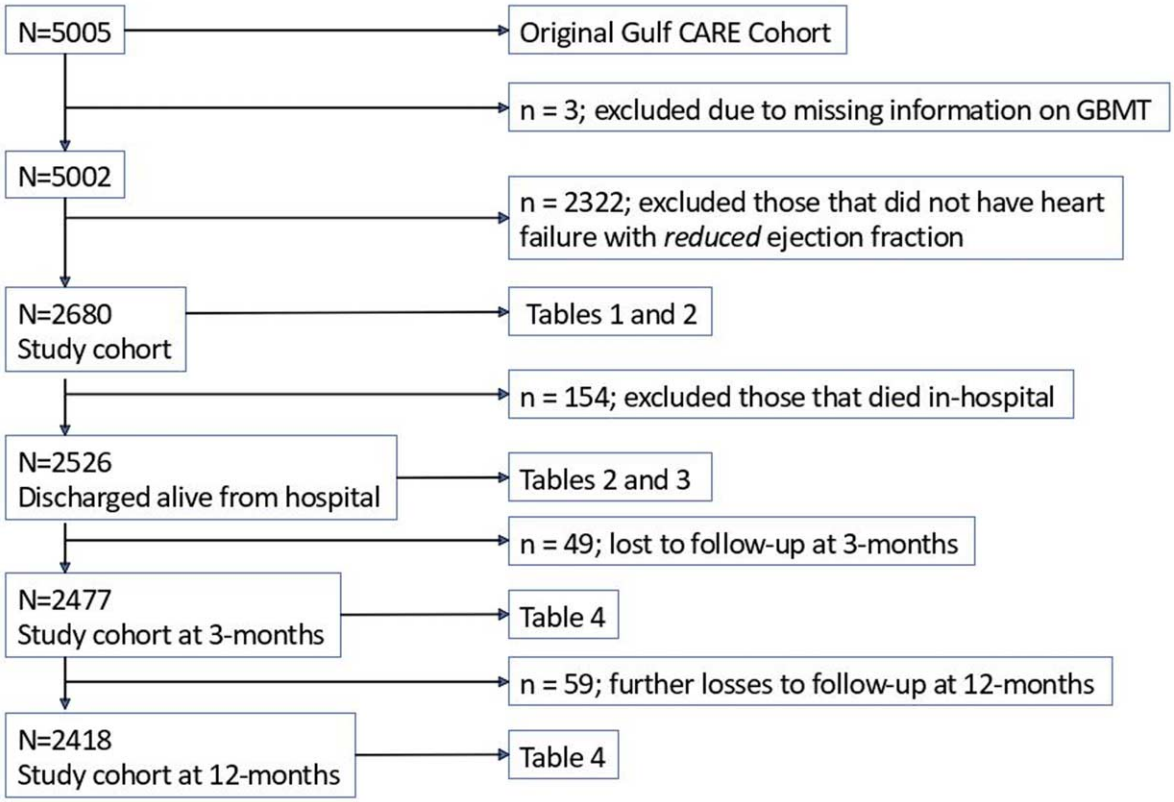

Figure 1. Summary of patient selection and losses to follow-up. GBMT, guideline-based medical therapy.

hospitalization for HF. De novo acute HF was defined as acute HF in patients with no prior history of HF.

2.2. Exclusion criteria

Patients with HF who were discharged from the emergency room without admission were excluded. Patients transferred from a non-registry hospital and those from whom informed consent could not be obtained were also excluded. Patients whose final diagnosis was not HF, and those who had a preserved ejection fraction of >40% were also excluded from the final analyses.

2.3. Outcomes measures

As per the objectives, the main outcomes measures included the numbers and types of GBMT use (RAS blockers, b-blockers, and MRAs), their predictors as well as the impact of GBMT use on 3-month and 12-month all-cause cumulative mortality as elaborated in the statistical analysis section. Optimum target doses attainments were based on the American (ACC) and European (ESC) HF guidelines.[26–28]

2.4. Statistical analysis

Descriptive statistics were used to summarize the data. For categorical variables, frequencies and percentages were reported, and differences between groups were analysed using Pearson's χ^2 test (or Fisher's exact test for expected cells <5). For continuous variables, the mean and standard deviation (SD) were used to summarize the data, while comparative analyses were done using ordinary least squares (OLS) regression. Analyses of multivariate predictors of GBMT for HF employed multiple logistic regression utilizing stepwise-backwards elimination method adjusting for age, gender, khatt use, smoking, alcohol, body mass index, hypertension, diabetes mellitus, prior stroke/transient ischemic attack (TIA), chronic kidney disease (CKD)/dialysis, heart rate (HR) on admission, systolic blood pressure (BP) and diastolic BP on admission, in-hospital percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), prior medications (beta blocker, statin, aspirin, clopidogrel, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, aldosterone antagonist) for the in-hospital model while for the 3- and 12-months logistic models, medications at hospital discharge were used. An a priori two-tailed level of significance was set at a *P*-value of .05. Statistical analyses were conducted using STATA version 13.1 (STATA Corporation, College Station, TX).

3. Results

From the original Gulf CARE cohort of 5005 patients, this study included a total of 2680 patients who had HFrEF. These patients had an overall mean age of 58 ± 15 years, 72% (n = 1936) were males, 25% (n = 673) were smokers (including chewing tobacco and/or smoking water-pipe), 18% (n = 481) chewed khatt, and 4.2% (n = 112) were daily alcohol consumers. The three most common co-morbidities were coronary artery disease (CAD) (62%; *n* = 1650), hypertension (57%; *n* = 1538), and diabetes mellitus (47%; *n* = 1267). The majority of patients had ADCHF (61%; *n* = 1629). The majority of patients were on dual (39%;

Table 1

Patient characteristics of the acute heart failure cohort with *reduced* ejection fraction (HFrEF, <40%) stratified by the number of guideline-based medical therapy (GBMT).

Characteristic, n (%) unless specified otherwise	All (n = 2680)	Number of GBMT medications				P
		0 (n = 193; 7.2%)	1 (n = 375; 14%)	2 (n = 1057; 39%)	3 (n = 1055; 39%)	
Demographic						
Age, mean ± SD, years	58 ± 15	59 ± 16	63 ± 14	60 ± 14	55 ± 14	<.001
Male gender	1936 (72%)	136 (70%)	261 (70%)	759 (72%)	780 (74%)	.360
Smoking*	673 (25%)	35 (18%)	68 (18%)	263 (25%)	307 (29%)	<.001
Khatt	481 (18%)	20 (10%)	17 (4.5%)	130 (12%)	314 (30%)	<.001
Alcohol†	112 (4.2%)	8 (4.2%)	14 (3.7%)	59 (5.6%)	31 (2.9%)	.024
BMI, mean ± SD, kg/m^2	27.5 ± 5.6	27.1 ± 5.3	27.9 ± 5.6	27.6 ± 5.7	27.3 ± 5.5	.195
Medical history						
CAD	1650 (62%)	132 (69%)	255 (68%)	729 (69%)	534 (51%)	<.001
PVD	125 (4.7%)	10 (5.2%)	20 (5.3%)	55 (5.2%)	40 (3.8%)	.393
Afib	306 (11%)	18 (9.3%)	38 (10%)	118 (11%)	132 (13%)	.430
Stroke/TIA	225 (8.4%)	20 (10%)	46 (12%)	107 (10%)	52 (4.9%)	<.001
Hypertension	1538 (57%)	115 (60%)	263 (70%)	653 (62%)	507 (48%)	<.001
Dyslipidemia	948 (35%)	74 (38%)	144 (38%)	432 (41%)	298 (28%)	<.001
Diabetes mellitus	1267 (47%)	104 (54%)	233 (62%)	532 (50%)	398 (38%)	<.001
CKD/dialysis	370 (14%)	51 (26%)	122 (33%)	146 (14%)	51 (4.8%)	<.001
Asthma/COPD	199 (7.4%)	16 (8.3%)	50 (13%)	79 (7.5%)	54 (5.1%)	<.001
Sleep apnea‡	33 (1.2%)	1 (0.5%)	13 (3.5%)	9 (0.9%)	10 (1.0%)	.003
Valvular heart disease	301 (11%)	24 (12%)	36 (10%)	122 (12%)	119 (11%)	.709
Clinical presentation						
HR, mean ± SD, bpm	77 ± 13	73 ± 27	79 ± 13	78 ± 12	76 ± 11	<.001
SBP, mean ± SD, mmHg	133 ± 32	121 ± 37	137 ± 32	134 ± 32	131 ± 31	<.001
BG, mean ± SD, mmol/L	9.8 ± 6.1	11.0 ± 7.0	10.3 ± 5.6	9.9 ± 5.7	9.3 ± 6.4	<.001
Crea, mean ± SD, μmol/L	130 ± 112	180 ± 143	162 ± 149	128 ± 107	112 ± 87	<.001
eGFR, mean ± SD, ml/min	67 ± 32	53 ± 35	58 ± 35	69 ± 33	73 ± 29	<.001
LVEF, mean ± SD, %	27 ± 7	27 ± 7	28 ± 7	28 ± 7	27 ± 7	<.001
In-hospital management						
PCI/CABG	232 (8.7%)	15 (7.8%)	41 (11%)	113 (11%)	63 (6.0%)	<.001
In-hospital course treatment§	1205 (45%)	167 (87%)	205 (55%)	426 (40%)	407 (39%)	<.001
Heart failure type						
De novo heart failure	1051 (39%)	81 (42%)	138 (37%)	386 (37%)	446 (42%)	.31
ADCHF	1629 (61%)	112 (58%)	237 (63%)	671 (63%)	609 (58%)	
NYHA functional class						
2–4	2578 (96%)	185 (96%)	361 (96%)	1013 (96%)	1019 (97%)	.830
Main physician						
Cardiologist	2046 (76%)	123 (64%)	264 (70%)	783 (74%)	876 (83%)	<.001
Internist	634 (24%)	70 (36%)	111 (30%)	274 (26%)	179 (17%)	

Statistical analyses were performed using ordinary least squares (OLS) regression and Pearson's χ^2 test, wherever appropriate. GBMT, defined as renin-angiotensin system (RAS) blocker, a beta-blocker and a mineralocorticoid antagonist (MRA).

ADCHF = acute decompensated chronic heart failure, Afib = atrial fibrillation, BG = baseline admission blood glucose, BMI = body mass index, bpm = beats per minute, CABG = coronary artery bypass graft, CAD = coronary artery disease, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, Crea = serum creatinine, eGFR = estimated glomerular filtration rate (n = 2621), HR = heart rate (n = 2583), kg = kilogram, LVEF = LV ejection fraction, NYHA = New York Heart Association functional class, PCI = percutaneous coronary intervention, PVD = peripheral vascular disease, SBP = systolic blood pressure (n = 2603), SD = standard deviation, TIA = transient ischemic attack.

* Smoking, includes chewing tobacco and/or smoking water-pipe

† Alcohol, drinking daily

‡ Sleep apnea, only in those on therapy

§ In-hospital course treatment included non-invasive ventilation, intubation/ventilation, cardiogenic shock, inotropes, intra-aortic balloon pump, acute dialysis/ultrafiltration, atrial fibrillation requiring therapy, major bleeding, blood transfusion, stroke, and systemic infection requiring therapy.

n = 1057) and triple (39%; *n* = 1055) GBMT modalities, 14% (n = 375) received only one GBMT medication, while 7.2% (n = 193) were not on any GBMT medications (Table 1). Out of the cohort, only 8.8% (n = 236) of the patients had recorded B-type natriuretic peptide (BNP), of whom 99% (234/236) had BNP values of ≥100 pg/mL. Additionally, elevated troponin was reported in 41% (1012/2454) of the patients (*data for BNP and elevated troponin are not shown in*Table 1). At 12-months post-discharge, follow-up was complete in 2,418 (90.2%) patients, after excluding patients who died in-hospital (5.7%), and those lost to follow-up (4.0%). For a detailed patient flow including exclusions and losses to follow-up, please refer to Figure 1.

When compared to patients on single medication, those on the triple GBMT combination were younger (55 vs 63 years; $P < .001$) but more likely to be smokers (29% vs 18%; $P < .001$) and khatt users (30% vs 4.5%; $P < .001$). However, they were less likely to have associated co-morbidities such as CAD (51% vs 68%; $P < .001$), stroke/TIA (4.9% vs 12%; $P < .001$), hypertension (48% vs 70%; $P < .001$), dyslipidemia (28% vs 38%; $P < .001$), diabetes mellitus (38% vs 62%; $P < .001$),

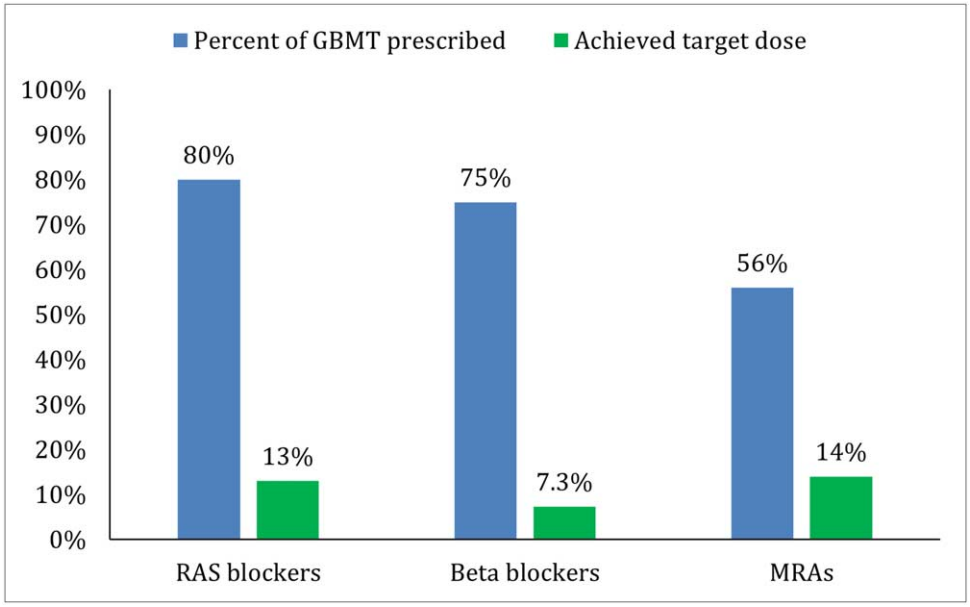

Figure 2. The percentage of patients on guideline-based medical therapies (GBMTs) and the percentage of patients on target doses of GBMTs. RAS = renin-angiotensin system, MRA = mineralocorticoid antagonist.

CKD/dialysis (4.8% vs 33%; $P < .001$), asthma/chronic obstructive pulmonary disease (COPD) (5.1% vs 13%; $P < .001$), and sleep apnea requiring therapy (1.0% vs 3.5%; $P = .003$) (Table 1). On admission, patients on the triple GBMT medications (in comparison with patients on single medication), presented with lower HR (76 vs 79 beats/min; $P < .001$), systolic BP (131 vs 137 mmHg; $P < .001$), blood glucose (9.3 vs 10.3 mmol/L; $P < .001$), creatinine (112 *vs* 162 μmol/L; $P < .001$), and higher estimated glomerular filtration rate (eGFR) (73 vs 58 ml/min/; $P < .001$) (Table 1). In comparison to patients on a single GBMT medication, those on the triple GBMT medications were less likely to be managed with in-hospital PCI/CABG (6.0% vs 11%; $P < .001$) and in-hospital courses (i.e., infection requiring therapy, requirement for inotropes, and non-invasive ventilation (39% vs 55%; $P < .001$)). Patients on the triple GBMT were more likely to be looked after by a cardiologist, as their main physician, rather than an internist (83% vs 17%; $P < .001$) (Table 1), and to be discharged with diuretics (98% vs 94%; $P < .001$) and digoxin (41% vs 25%; $P < .001$) (Table 2), compared to patients on a single GBMT medication.

Of the 2680 patients with HFrEF on the Gulf CARE registry, the majority were receiving GBMT on admission (RAS blockers

Table 2

Other medications of the acute heart failure cohort with *reduced* ejection fraction (<40%) stratified by the number of guideline-based medical therapy (GBMT).

		Number of GBMT medications				
Medications, *n (%)*	**All (N = 2680)**	**0 (n = 193)**	**1 (n = 375)**	**2 (n = 1057)**	**3 (n = 1055)**	***P***
Pre-hospitalization medications						
Diuretics	1604 (60%)	118 (61%)	230 (61%)	651 (62%)	605 (57%)	.207
Digoxin	581 (22%)	57 (30%)	64 (17%)	212 (20%)	248 (24%)	.001
Oral nitrates	717 (27%)	64 (33%)	129 (34%)	275 (26%)	249 (24%)	<.001
CCB	198 (7.4%)	16 (8.3%)	46 (12%)	93 (8.8%)	43 (4.1%)	<.001
Aspirin	1714 (64%)	109 (56%)	255 (68%)	697 (66%)	653 (62%)	.011
Clopidogrel	519 (19%)	37 (19%)	88 (23%)	213 (20%)	181 (17%)	.051
Ivabradine	78 (2.9%)	7 (3.6%)	8 (2.1%)	31 (2.9%)	32 (3.0%)	.751
Discharge medications[*] (N = *2526*)						
Diuretics	2423 (96%)	65 (82%)	339 (94%)	985 (95%)	1034 (98%)	<.001
Digoxin	866 (34%)	21 (27%)	92 (25%)	320 (31%)	433 (41%)	<.001
Oral nitrates	985 (39%)	34 (43%)	173 (48%)	429 (41%)	349 (33%)	<.001
CCB	188 (7.4%)	13 (16%)	59 (16%)	84 (8.1%)	32 (3.0%)	<.001
Aspirin	2082 (82%)	64 (81%)	303 (84%)	871 (84%)	844 (80%)	.108
Clopidogrel	944 (37%)	31 (39%)	155 (43%)	440 (43%)	318 (30%)	<.001
Ivabradine	159 (6.3%)	9 (11%)	23 (6.4%)	72 (7.0%)	55 (5.2%)	.100

GBMT = defined as renin-angiotensin system (RAS) blocker, a beta-blocker and a mineralocorticoid antagonist (MRA), CCB = calcium channel blocker.
Analyses were performed using Pearson's chi-square test.
[*] Discharge medications excluded for patients who died in-hospital (n = 154)

Table 3

Multivariate predictors of guideline-based medical therapy use for the treatment of heart failure.

	RAS blocker		β-blocker		MRA		GBMT	
Characteristic	**aOR**	***P***	**aOR**	***P***	**aOR**	***P***	**aOR**	***P***
Female gender	1.02	.863	0.97	.789	0.96	.655	0.88	.217
Age, per 10 years	1.04	.469	0.95	.263	0.85	<.001*	0.86	<.001*
BMI, per kg/m^2	1.01	.330	0.99	.185	1.01	.257	1.00	.701
Systolic BP, per 10 mmHg	1.03	.143	1.03	.084	0.94	<.001*	0.98	.121
NYHA functional class, ≥2	1.45	.190	0.77	.373	1.49	.081	1.30	.275
Heart rate, per 10 beats/min	1.04	.159	0.99	.717	1.03	.174	1.04	.062
eGFR, per ml/min	1.02	<.001*	1.01	.021*	1.00	.264	1.00	.745
Ischemic heart failure	1.08	.567	0.91	.419	0.69	<.001*	0.76	.005*
Hypertension	1.07	.637	1.23	.099	0.73	.004*	0.91	.378
Diabetes mellitus	0.81	.118	0.84	.125	0.78	.011*	0.76	.007*
Asthma/COPD	1.07	.752	0.29	<.001*	1.26	.173	0.73	.086
CKD/dialysis	0.28	<.001*	1.22	.241	0.31	<.001*	0.26	<.001*
Cardiologist#	1.17	.251	2.83	<.001*	1.41	.001*	2.00	<.001*

GBMT = guideline-based medical therapy, defined as the concurrent administration of a renin-angiotensin system (RAS) blocker, a b-blocker and a mineralocorticoid antagonist (MRA). aOR = adjusted odds ratio, BMI = body mass index, BP = blood pressure, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, eGFR = estimated glomerular filtration rate, kg = kilogram, NYHA = New York Heart Association functional class.

Analyses were performed using multiple logistic regression models using the simultaneous method and only those were discharged alive after the *index* admission (N = 2526).

cardiologist versus an internist as the main caregiver.

* significant at $P < .05$

80%, b-blockers 75%, MRAs 56%). However, only a small proportion of these patients were taking target doses of these medications (RAS blockers 13%, b-blockers 7.3%, MRAs 14%; Fig. 2). For a detailed list of medications used by all patients, see Table 2. A total of 3.1% (n = 82) of the patients were on implantable cardiac defibrillators (28 on cardiac resynchronization therapy defibrillator (CRT-D), one on cardiac resynchronization therapy pacemaker (CRT-P), 48 on implantable cardioverter defibrillator (ICD), and five on permanent pacemaker (PPM)) (*data not shown*).

After adjusting for multiple factors using a multivariate logistic model, older age ($P < .001$) and comorbidities such as ischemic HF ($P = .005$), diabetes mellitus ($P = .007$) and CKD/dialysis ($P < .001$) were identified as significant independent factors associated with not being prescribed the triple GBMT combination (Table 3). On the other hand, patients whose treatment was primarily managed by cardiologists were more likely to be prescribed the triple GBMT combination ($P < .001$; Table 3). A full list of independent factors associated with the use of RAS blockers, b-blockers and MRAs is outlined in Table 3.

There was a significant reduction in all-cause mortality both at 3-months (adjusted odds ratio (aOR) 0.48; 95% confidence interval (CI): 0.23–0.99; $P = .048$), and at 12-months (aOR 0.42; 95% CI: 0.23–0.74; $P = .003$) in patients taking the triple GBMT combination in comparison to those not taking any GBMT medication (Table 4). There was a trend for a reduction in the adjusted odds ratios (aORs) for both 3-month and 12-month all-cause mortality with increasing number of GBMT medications

Table 4

Impact on the number of guideline-based medical therapy (GBMT) prescribing after hospital discharge on 3-month and 1-year mortality of the acute heart failure cohort with *reduced* ejection fraction (<40%).

		Number of GBMT medications			
Mortality	**All (N = 2477*)**	**0 (n = 77)**	**1 (n = 351)**	**2 (n = 1018)**	**3 (n = 1031)**
3-month, *n* (%)	183 (7.4%)	12 (15.6%)	34 (9.7%)	73 (7.2%)	64 (6.2%)
aOR [95% CI]		1	0.66 [0.31-1.39]	0.50 [0.25-1.02]	0.48 [0.23-0.99]
P-value		Reference	*P* = .271	*P* = .057	*P* = .048
HL *P*-value	0.218				
ROC	0.71				
12-month, *n* (%)	392 (16.2%)	22 (29.3%)	73 (21.6%)	169 (17.0%)	128 (12.6%)
aOR [95% CI]		1	0.63 [0.35-1.15]	0.50 [0.29-0.89]	0.42 [0.23-0.74]
P-value		Reference	*P* = .130	*P* = .018	*P* = .003
HL *p*-value	0.693				
ROC	0.71				

Reported percentage values are column percentages. Multivariate analyses were conducted using logistic regression model utilizing stepwise-backwards elimination method adjusting for age, gender, khatt use, smoking, alcohol, body mass index, hypertension, diabetes mellitus, prior stroke/transient ischemic attack, chronic kidney disease or dialysis, heart rate on admission, systolic and diastolic blood pressure on admission, in-hospital percutaneous coronary intervention or coronary artery bypass graft, prior medications (beta blocker, statin, aspirin, clopidogrel, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, aldosterone antagonist) for the in-hospital model while for the 3- and 12-months logistic models, medications at hospital discharge were used.

GBMT, defined as renin-angiotensin system (RAS) blocker, a beta-blocker and a mineralocorticoid antagonist (MRA); aOR, adjusted odds ratio; CI, confidence interval; HL, Hosmer & Lemeshow; ROC, area under the receiver operating curve also known as *c*-statistic.

* Excluded patients who died in-hospital (n = 154) as well as those that were lost to follow-up at 3-months (n = 49; N = 2477) and a further 59 patients at 12-months (N = 2418).

from 0 to 3 (Table 4). There were no significant interactions between age and the number of GBMTs in terms of all-cause mortality at 3-months ($P = .927$), or at 12-months ($P = .309$).

4. Discussion

We report several key findings in this analysis on current use and predictors of GBMT, as well as their impact on survival in patients with acute HFrEF. Of the 2680 patients with HFrEF on the Gulf CARE registry, the majority were on dual (39%) and triple (39%) GBMT, while 7.2% of patients did not receive any GBMT medications. GBMT was achieved as follows: RAS blockers, 80%; b-blockers, 75%; MRAs, 56%. Despite the majority of Gulf CARE patients receiving GBMT on admission, target doses were achieved in only a minority of these patients (RAS blockers 13%, b-blockers 7.3%, MRAs 14%). In terms of in-hospital management, patients on the triple GBMT were less likely than those on single GBMT to require interventions such as PCI/CABG or in-hospital courses including infection requiring therapy, requirement for inotropes, and non-invasive ventilation. Having a cardiologist as the main treating physician was associated with increased likelihood of patients being prescribed triple GBMT. On the other hand, patients with ischemic HF, diabetes mellitus and CKD/dialysis were significantly less likely to receive triple GBMT. Advanced age was associated with decreased use of triple GBMT; however, there was no significant interaction between age and the number of GBMT for 3-month or 12-month mortality.

Utilization of GBMT in patients from the Gulf CARE registry (RAS blockers, 80%; b-blockers, 75%; MRAs, 56%) was found to be more or less similar to previous studies. For example, the CHAnge the Management of Patients with Heart Failure (CHAMP-HF) registry reported the use of RAS blockers in 74% and b-blockers in 66% of its 3095 patients from 151 US practice sites.[37] Another study which assessed 370 patients with HFrEF from two centres in Canada, reported that 86.4% were prescribed RAS blockers, 93.4% b-blockers and 44.7% MRAs.[38] Valika and colleagues reported that 74.3% of their 244 patients with HFrEF were using ACE inhibitors, 95.4% were using b-blockers and 34% were using MRAs.[39] A Turkish study of 1462 patients with HFrEF recruited from 24 centers reported that 78.2%, 90.2%, and 55.4% of patients received treatment with RAS blockers, b-blockers and MRAs, respectively.[40] In comparison to these studies, the use of RAS blockers and MRAs in Gulf CARE patients was either similar or higher; however, b-blockers were less utilized.

The lack of treatment of HFrEF with GBMT and/or treatment with suboptimal dosages are associated with increased morbidity,[30,31] hence it is recommended by the ACC that HFrEF patients should be treated with the maximally tolerated doses of appropriate GBMT.[26,28] Target doses of GBMT were achieved in only a minority of patients from the Gulf CARE registry (RAS blockers 13%, b-blockers 7.3%, MRAs 14%). Suboptimal dosing in patients with HFrEF is a well-known phenomenon which has been reported by several previous studies.[29,37,39–41]

The positive impact of treatment of Gulf CARE patients with acute HFrEF with ACE inhibitors or ARBs in terms of reduced mortality risk has been previously reported.[42] In this study, we report multiple significant benefits to being treated with three GBMT medications in comparison to a single medication in Gulf CARE patients with HF*r*EF. These benefits included decreased 3-month and 12-month mortality, similar to previous studies,[18–25,39,43] decreased HR, systolic BP, blood glucose and creatinine, and improved eGFR on follow-up. Comorbidities such as CAD, dyslipidemia, diabetes mellitus, CKD, asthma/COPD and sleep apnea requiring therapy were more likely to be present in patients on a single GBMT in comparison to those taking triple GBMT. In terms of in-hospital management, patients on the triple GBMT were less likely than those on single GBMT to require interventions such as PCI/CABG or in-hospital course, suggesting pharmacological management with triple GBMT can help reduce the need for serious interventions. The reasons underlying suboptimal utilization and dosing of GBMT in HFrEF patients from the Gulf region remain unclear and require further investigation. However, as mentioned earlier, low utilization and under-dosing of GBMT is not specific to the Gulf region and has been reported worldwide by several studies.[29,40,41] Owing to this global observation of under-utilization of evidence-based life-prolonging treatments, and dosing below trial-proven doses, Packer and Metra in a recent review article argue that GBMT for HFrEF does not exist.[44] They propose a framework that promotes forced-titration strategies and prescriber self-awareness regarding the lack of evidence supporting the currently prevalent prescribing of sub-target doses.[44]

Our data demonstrated that cardiologist involvement in care was associated with increased prescribing of triple GBMT, this finding is supported by a Canadian study mentioned above which also found cardiologist intervention to be associated with increased prescribing of GBMT as well as increased target dosing of GBMT.[38] It is possible that the increased likelihood of patients being discharged with diuretics and digoxin may be related to having a cardiologist involved in care; however, this association was not investigated in the current study.

Patients with comorbid ischemic HF, diabetes mellitus and CKD/dialysis were significantly less likely to receive triple GBMT. When investigated individually, there was no significant reduction in the prescribing of RAS blockers or b-blockers for ischemic HF or diabetes, but there was significant reduction in the prescribing of MRAs in patients with these comorbidities. For patients with CKD/dialysis, both RAS blockers and MRAs were less likely to be prescribed. This is not surprising given that both classes of medication are to be used with caution with impaired renal function.[27] B-blockers were also less prescribed to HFrEF patients with asthma/COPD, probably because even cardio-selective b-blockers can precipitate bronchospasms, especially if asthma/COPD is not well controlled.[45]

Another significant predictor of GBMT use in patients with HFrEF was age which has been previously reported[46]; advanced age was associated with decreased use of triple GBMT. Our analysis showed no significant interaction between age and the number of GBMT for 3-month or 12-month mortality. Hence, the benefits of being on triple GBMT should not be affected by age, and older patients could derive as much benefit as younger patients from the triple therapy. This is an important finding as it should encourage prescribers, including cardiologists, to increase prescribing triple GBMT regardless of patient of age, and to aim to reach the appropriate target doses in order to obtain the maximum possible benefits of therapy in patients with HFrEF.

There are some limitations to the current study. Firstly, as this registry relates to data captured in 2012, recent therapeutic GBMT modalities such as sacubritil/valsartan, sodium-glucose cotransporter 2 inhibitor and oral soluble guanylate cyclase

stimulator were missing. However, recently published data on AHF in the region also did not mention these newer GBMT modalities.[34] Secondly, certain information were unavailable including the duration or compliance of use of the GBMT medications prior to hospital admission, as well as contra-indications and adverse events to certain medications which may have led to lower utilization of GBMT. Moreover, compliance to medications at 12-months was not validated. Thirdly, given that GBMT dosages were reported in an inpatient setting, the reported under-dosing may be inaccurate, since up-titration of the doses usually occurs in the outpatient setting. Therefore, the doses of the prescribed GBMT may in fact be closer to guideline recommendations than reported in this study. Fourthly, while cardiovascular mortality may have been the most relevant type of mortality rate to report, we only had the data to report all-cause mortality. In saying that, all-cause mortality was reported in-hospital, at 3-months and 12-months. Fifthly, echocardiographic data and pro-BNP measurements were missing in the majority of the patients, and LVEF was not measured at the 3-months and 12-months follow-up visits. Lastly, the study design was retrospective, therefore it may have inherently introduced self-selection biases, for example, analysis being confounded by severity of disease or comorbidities.

5. Conclusion

The proportion of patients with HFrEF in the Arabian Gulf taking triple GBMT was suboptimal, with only a small proportion of patients reaching target doses. The use of triple GBMT, in comparison to single GBMT, was associated with decreased 3-month and 12-month mortality. There were several significant predictors for triple GBMT; patients were less likely to receive GBMT if they were older, or had comorbidities such as ischemic HF, diabetes mellitus or CKD/dialysis. Finally, having a cardiologist as their main caregiver increased the likelihood of being prescribed triple GBMT. Nonetheless, prescribing of triple pharmacotherapy for HFrEF in the Arabian Gulf was underutilized, and dosing was suboptimal. Continuing education initiatives are required to facilitate increased implementation of guideline-recommended prescribing and evidence-based dosing, encouraging timely up-titration to target doses in patients with HFrEF, including those older in age. Team-based care approaches including a pharmacist may improve initiation, up-titration and compliance to medication of HF patients.[47]

Acknowledgments

The authors thank the patients who consented to participate in this study as well as the medical staff involved from the seven Gulf countries. Publication of this manuscript was supported by Mohammed Bin Rashid University of Medicine and Health Sciences (MBRU).

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