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### ► To cite this version:

Kensuke Matsushita, Clément Delmas, Benjamin Marchandot, François Roubille, Nicolas Lamblin, et al.. Optimal Heart Failure Medical Therapy and Mortality in Survivors of Cardiogenic Shock: Insights From the FRENSHOCK Registry. *Journal of the American Heart Association*, 2024, 13 (5), pp.e030975. 10.1161/JAHA.123.030975 . hal-04474986

**HAL Id: hal-04474986**

**<https://hal.science/hal-04474986v1>**

Submitted on 10 Mar 2024

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# Optimal Heart Failure Medical Therapy and Mortality in Survivors of Cardiogenic Shock: Insights From the FRENSHOCK Registry

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**Keywords:**

cardiogenic shock; guideline-directed medical therapy; heart failure; left ventricular ejection fraction; mortality.

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**Nonstandard Abbreviations and Acronyms**

<b>CS</b>	cardiogenic shock
<b>GDMT</b>	guideline-directed heart failure medical therapy
<b>MRA</b>	mineralocorticoid receptor antagonist
<b>RASI</b>	renin-angiotensin system inhibitor

## Abstract

**Background:**

The effects of pharmacological therapy on cardiogenic shock (CS) survivors have not been extensively studied. Thus, this study investigated the association between guideline-directed heart failure (HF) medical therapy (GDMT) and one-year survival rate in patients who are post-CS.

**Methods and results:**

FRENSHOCK (French Observatory on the Management of Cardiogenic Shock in 2016) registry was a prospective multicenter observational survey, conducted in metropolitan French intensive care units and intensive cardiac care units. Of 772 patients, 535 patients were enrolled in the present analysis following the exclusion of 217 in-hospital deaths and 20 patients with missing medical records. Patients with triple GDMT (beta-blockers, renin-angiotensin system inhibitors, and mineralocorticoid receptor antagonists) at discharge (n=112) were likely to have lower left ventricular ejection fraction on admission and at discharge compared with those without triple GDMT (n=423) (22% versus 28%,  $P<0.001$  and 29% versus 37%,  $P<0.001$ , respectively). In the overall cohort, the one-year mortality rate was 23%. Triple GDMT prescription was significantly associated with a lower one-year all-cause mortality compared with non-triple GDMT (adjusted hazard ratio 0.44 [95% CI, 0.19-0.80];  $P=0.007$ ). Similarly, 2:1 propensity score matching and inverse probability treatment weighting based on the propensity score demonstrated a lower incidence of one-year mortality in the triple GDMT group. As the number of HF drugs increased, a stepwise decrease in mortality was observed (log rank;  $P<0.001$ ).

**Conclusions:**

In survivors of CS, the one-year mortality rate was significantly lower in those with triple GDMT. Therefore, this study suggests that intensive HF therapy should be considered in patients following CS.

Cardiogenic shock (CS) is a life-threatening state of hypoperfusion caused by inadequate cardiac output, often resulting in multiorgan failure. Cardiac insult causing severe cardiac dysfunction may be caused by an acute loss of myocardial tissue (eg, acute myocardial infarction) or may be the natural progression of advanced heart failure (HF), specific precipitants, or both.<sup>1</sup> The in-hospital mortality rates in patients with CS range between 30% and 60%, 1-year mortality rates between 50% and 60%.<sup>1, 2</sup> Recent studies have confirmed such a high overall mortality in spite of more invasive management.<sup>3, 4, 5</sup>

Sodium glucose cotransporter 2 (SGLT2) inhibitors have been recently recommended among the first-line treatments of chronic HF.<sup>6</sup> Until 2021, guideline-directed heart failure medical therapy (GDMT) for patients with HF with reduced ejection fraction (EF) comprised 3 HF drugs: beta blockers, renin-angiotensin system inhibitors (RASi), and mineralocorticoid receptor antagonists (MRA), which have significantly reduced mortality.<sup>7</sup> More important here, the initiation of evidence based oral medical treatment has been recommended before discharge in patients with acute HF.<sup>6</sup> However, the impact of GDMT on survival in patients who are post-CS has not been specifically investigated. Thus, this study assessed the impact of the triple GDMT at discharge in survivors of CS to delineate the necessity of HF therapy during the post-CS phase.

## METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

### Patient Population and Study Design

FRENSHOCK (French Observatory on the Management of Cardiogenic Shock in 2016) was a prospective multicenter registry of patients with CS conducted in metropolitan France between April and October 2016 in intensive cardiac care units and intensive care units (NCT02703038), which enrolled 772 patients from 49 participating centers. Inclusion criteria were as follows: patients aged  $\geq 18$  years old with at least 1 of each of the following 3 components: (1) hemodynamic criteria, defined as a systolic blood pressure  $< 90$  mm Hg or the need for maintenance with vasopressors/inotropes or a cardiac index  $< 2.2$  L/min per m<sup>2</sup>; (2) elevated left or right heart pressure, defined by clinical signs, radiology, blood tests, echocardiography, or invasive hemodynamic overload signs; and (3) signs of organ malperfusion, which could be clinical or biological. Patients admitted after cardiopulmonary resuscitation were included if they fulfilled the defined CS criteria. Patients could be included regardless of the CS cause, and whether the CS was initial or secondary. Exclusion criteria were the refusal or inability to consent and a diagnosis of CS refuted in favor of alternative diagnoses, such as septic shock, refractory cardiac arrest, and postcardiotomy CS. The details of the methods used for this registry were previously published.<sup>3, 8</sup>

### Data Collection

The study was conducted in accordance with the Declaration of Helsinki and French law. Written informed consent was obtained from all the patients. The handling and storage of the recorded data were reviewed and approved by the Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé (French Health Research Data Processing Advisory Committee) (no. 15.897) and the Commission nationale de

l'informatique et des libertés (French Data Protection Agency; no. DR-2016-109). Data on baseline characteristics including demographics, risk factors, medical history, clinical triggers, and in-hospital data were collected as previously described.<sup>3, 8</sup> Clinical outcomes were obtained directly by local investigators.

## Definition of Guideline-Directed Medical Therapy

In this study, triple GDMT was defined as the concurrent prescription of 3 HF medication classes including beta blockers, RASI, and MRA. This analysis considered the prescription of an angiotensin receptor-neprilysin inhibitor in the category of RASI.<sup>9</sup> Due to the study period, the data collection of the use of SGLT2-inhibitors was not performed. Patients with missing data regarding GDMT were excluded from the analysis.

## Study End Point and Follow-Up

The follow-up was completed on the last medical interview date, the last examination date, or the date when the end point event occurred. At 1 year, the follow-up was performed using the following sequential procedures: first, consult the registry office of the patient's birthplace for death certificates; next, contact the patient's general practitioner or cardiologist; and finally, contact the patient or their direct relatives. In many instances, written contact was followed by a telephone interview with the patients or their families to clarify the presence of left ventricular or biventricular assist device, heart transplantation, or ongoing treatment. The primary end point of the present study was 1-year all cause mortality.

## Statistical Analysis

Categorical variables are represented as frequencies and percentages, and continuous variables are expressed as mean $\pm$ SD or median and interquartile values. Differences between the 2 treatment groups were assessed with  $\chi^2$  tests or Fisher exact tests for categorical variables. Continuous variables with normal distributions were compared between groups using Unpaired Student's *t* test. Wilcoxon test was used to analyze continuous variables with skewed distributions. The primary end point was compared with the use of a log-rank test and the hazard ratio (HR), with a 95% CI, was calculated from a Cox proportional hazard model. Factors associated with a *P* value <0.05 in the univariate analyses were included in the multivariate analyses. Another multivariate model was made based on known variables that may influence mortality following CS (age, body mass index, prior coronary artery bypass grafting, peripheral artery disease, stroke history, chronic renal disease, ischemic shock, lactate level, cardiac arrest, and left ventricular ejection fraction [LVEF] at discharge).<sup>10, 11, 12, 13, 14</sup> The 95% CI around the percentage attenuation was obtained by using a 1000-time bootstrap resampling. To avoid bias attributable to treatment selection caused by a lack of randomization, 2:1 propensity score matching and inverted probability of treatment weighting were used to address confounding and to estimate the average treatment effect in the triple GDMT population. A total of 11 covariables at baseline, which were assumed to influence the HF drug selection, were logistically regressed to the probability of receiving treatment: age, sex, smoking status, diabetes, hypertension, dyslipidemia, chronic renal failure, chronic obstructive pulmonary disease, active cancer, ischemic trigger, and LVEF on admission. For the propensity score matching, a nearest neighbor algorithm was used to match patients in the 2 groups in a 2:1 ratio, with a caliper width equal to 0.2 of the SD of the logit of the propensity score and without replacement. For the inverted probability of treatment weighting, each participant was weighted using overlap weights approach, which down weights individuals on the basis of propensity score values. The absolute standardized mean difference was used as a balance metric to summarize the difference between 2 univariate distributions of a single variable. A value  $\geq 0.10$  was considered as an indicator of imbalance. The effect of triple GDMT on the primary end point was also estimated within the propensity score match cohort and the weighted pseudo-population by log-rank test from the adjusted Kaplan–Meier

curves and adjusted HR from a Cox proportional hazard model. Finally, because some of the standardized mean differences were  $>0.1$ , we additionally performed doubly robust estimation, which requires constructing the propensity score-weighted regression model with additional baseline variables, to achieve consistent treatment effects. The propensity analyses produce the average treatment effect as the estimate of effect measure, which indicates the effect of triple GDMT versus non-triple GDMT at discharge in the scenario that non-triple GDMT was offered to patients who were discharged alive following CS (Table S1).<sup>15</sup> We used a quality assessment instrument to improve the conduct and reporting of our propensity score analyses (Table S2).<sup>16</sup> *P* values of  $<0.05$  were considered to indicate statistical significance. The analyses were performed using JMP Pro 17 software (SAS Institute, Cary, NC) or R version 3.6.3.<sup>17</sup> “matching,” “twang,” and “survival” packages of R were used for the propensity analyses.

## RESULTS

### Patient Characteristics

Of 772 patients, 237 patients were excluded from the current analysis due to either in-hospital death ( $n=217$ ) or missing medication records ( $n=20$ ) (Figure 1). Thus, 535 patients were enrolled in the analysis. Clinical characteristics are shown in Table 1. The mean age was  $64\pm 15$  years and 73% of the patients were male. Patients who received triple GDMT at discharge were more likely to be younger, current smokers, and under direct oral anticoagulants, MRA, or proton pump inhibitors on admission compared with patients without triple GDMT at discharge. Additionally, the incidence of chronic renal failure (known estimated glomerular filtration rate  $\leq 60$  mL/min per  $1.73$  m<sup>2</sup>) was lower in the triple GDMT group. Baseline cardiac disease was similar between the 2 groups. Initial clinical presentation, biological, and echocardiographic parameters are presented in Table S3. The triple GDMT group was associated with ischemic shock, higher estimated glomerular filtration rate, and hemoglobin levels. The rates of other triggers including arrhythmia, infection, and cardiac arrest were similar between the 2 groups. LVEF at baseline was significantly lower in the triple GDMT group (22% versus 28%,  $P<0.001$ ).

### In-Hospital Management and Complications

Fewer patients received volume expander, noninvasive respiratory support, renal replacement therapy, or heart transplantation in the triple GDMT group than in the non-triple GDMT group (Table 2 and Table S4). The incidence of in-hospital complications including infectious diseases, stroke, bleeding, and cardiac arrest were similar between the 2 groups (Table S5).

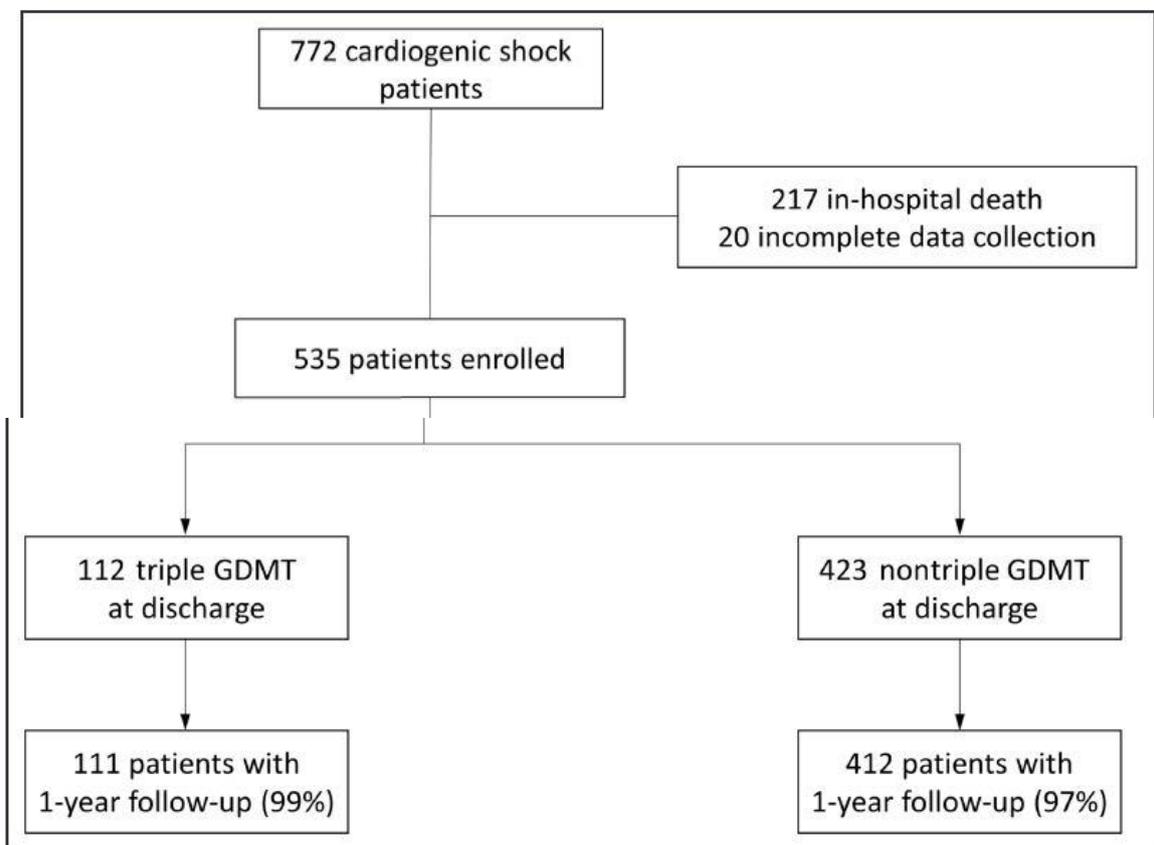
### Left Ventricular Ejection Fraction and Medications at Discharge

Lower LVEF at discharge was found in the triple GDMT group compared with the non-triple GDMT group (29% versus 37%,  $P<0.001$ ) (Table 2). Patients in the triple GDMT group were likely to receive P2Y<sub>12</sub> inhibitors, statins, direct oral anticoagulants, and diuretics at discharge.

### Impact of Triple Guideline-Directed Medical Therapy on 1-Year Clinical Outcomes

Clinical follow-up at 1 year was completed in 523 patients (98%). In the entire cohort, the 1-year mortality incidence was 23% (Table 3). There was no significant difference in the 1-year mortality rate between patients with ischemic triggers and those without (20% versus 24%,  $P=0.21$ ). Table 3 indicates that triple GDMT at discharge was significantly associated with lower mortality and heart

transplantation rates. Clinical data of unscheduled cardiovascular rehospitalization were available in 86% of the patients, which did not show any differences between the 2 groups. Kaplan–Meier curves of patients with and without triple GDMT on admission and at discharge are shown in Figure S1 and Figure 2A. Although the 1-year mortality rates of patients with and without triple GDMT on admission were similar (Figure S1), triple GDMT at discharge was significantly associated with lower 1-year mortality (Figure 2A). Notably, a stepwise decrease in 1-year mortality was observed when higher numbers of HF drugs were provided at discharge (Figure 3). Sub-analyses in patients who underwent LVEF evaluation at discharge (n=432) are shown in Figure S2. Patients with LVEF  $\leq$ 40% (n=306) had higher 1-year mortality compared with patients with LVEF  $>$ 40% (n=64) ( $P=0.01$ ). Although the beneficial effect of the triple GDMT therapy was similarly found in those 2 subgroups, statistical significance was found in the patients with LVEF  $\leq$ 40%, probably in part due to the larger number of patients.



**Figure 1.** Patient flow chart. GDMT indicates guideline-derived medical therapy.

**Table 1.** Patient Characteristics (Table view)

	Overall population (n=535)	Triple GDMT (n=112)	Nontriple GDMT (n=423)	P value
Age, y	64±15	61±15	65±14	0.004
Male	388 (73)	84 (75)	304 (72)	0.51
Body mass index, kg/m <sup>2</sup>	26.0±5.6	25.9±6.5	26.0±5.3	0.90
New York Heart Association classification (n=521)				0.37
1	192 (37)	47 (45)	145 (35)	
2	137 (26)	24 (22)	113 (27)	
3	126 (24)	26 (24)	100 (24)	
4	66 (13)	11 (10)	55 (13)	
History of cardiac disease				
Ischemic	156/419 (37)	28/93 (30)	128/326 (39)	0.11
Hypertrophic	9/300 (3)	4/71 (6)	5/229 (2)	0.22
Toxic	28/311 (9)	10/74 (14)	18/237 (8)	0.12
Idiopathic	52/339 (15)	8/76 (11)	44/263 (17)	0.19
Comorbidities				
Current smoker	155 (29)	41 (37)	114 (27)	0.045
Diabetes	154 (29)	34 (30)	120 (28)	0.69
Hypertension	247 (46)	43 (38)	204 (48)	0.06
Dyslipidemia	188 (35)	41 (37)	147 (35)	0.71
Pacemaker	38 (7)	9 (8)	29 (7)	0.67
Defibrillator	88 (16)	16 (14)	72 (17)	0.48
Coronary artery bypass grafting	37 (7)	8 (7)	29 (7)	0.92
Percutaneous coronary intervention	114 (21)	20 (18)	94 (22)	0.31
Peripheral artery disease	68 (13)	13 (12)	55 (13)	0.69

	Overall population (n=535)	Triple GDMT (n=112)	Nontriple GDMT (n=423)	P value
Stroke	37 (7)	10 (9)	27 (6)	0.35
Chronic renal failure	94 (18)	10 (9)	84 (20)	0.007
Dialysis	7 (1)	0 (0)	7 (2)	0.17
Chronic obstructive pulmonary disease	34 (6)	3 (3)	31 (7)	0.07
Active cancer	31 (6)	3 (3)	28 (7)	0.11
Previous medications				
Aspirin	201 (38)	42 (38)	159 (38)	0.99
P2Y12 inhibitors	91 (17)	19 (17)	72 (17)	0.99
Statins	198 (37)	40 (36)	158 (37)	0.75
Beta blockers	217 (41)	44 (39)	173 (41)	0.76
Vitamin K antagonist	100 (19)	15 (13)	85 (20)	0.11
Direct oral anticoagulants	44 (8)	16 (14)	28 (7)	0.009
Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers	197 (37)	44 (39)	153 (36)	0.54
Sacubitril/valsartan	14/507 (3)	2/106 (2)	12/401 (3)	0.54
Loop diuretics	245 (46)	51 (46)	194 (46)	0.95
Aldosterone antagonist	75 (14)	32 (29)	43 (10)	<0.001
Amiodarone	89/526 (16)	14/112 (13)	75/414 (18)	0.16
Proton pump inhibitor	191/531 (36)	29/112 (26)	162/419 (39)	0.01

Numbers of heart failure drugs on admission				<0.001
0	221/520 (43)	46/107 (43)	175/413 (42)	
1	139/520 (27)	23/107 (22)	116/413 (28)	
2	119/520 (23)	15/107 (14)	104/413 (25)	
3	41/520 (8)	23/107 (22)	18/413 (4)	
Clinical presentation at baseline				
Heart rate, bpm	95±30	97±27	94±31	0.27
Systolic BP, mm Hg	103±25	102±24	103±25	0.56
Diastolic BP, mm Hg	65±18	66±19	64±17	0.51
Estimated glomerular filtration rate, mL/min per 1.73 m <sup>2</sup>	49 (32–70)	57 (42–80)	48 (29–68)	<0.001
Total bilirubin, mg/L	16 (9–28)	15 (10–31)	16 (9–26)	0.91
N-terminal proBNP, pg/mL	7055 (3393–16 237)	6173 (3283–11 797)	8189 (3393–20 225)	0.29
BNP, pg/mL	1052 (435–2635)	1520 (668–2907)	996 (426–2451)	0.09
Lactate, mmol/L	2.8 (2.0–4.0)	2.3 (2.0–4.0)	3.0 (2.0–4.3)	0.26
Left ventricular ejection fraction, %	27±13	22±9	28±14	<0.001
Ischemic shock	189 (35)	51 (46)	138 (33)	0.01
Cardiac arrest	52 (10)	8 (7)	44 (10)	0.30

Values are n (%) or n/N (%), or mean±SD. BNP indicates brain natriuretic peptide; BP, blood pressure; and GDMT, guideline-derived medical therapy.

**Table 2.** In-Hospital Management, Left Ventricular Function Assessment, and Medication Records at Discharge (Table view)

	Overall population (n=535)	Triple GDMT (n=112)	Nontriple GDMT (n=423)	P value
Catecholamine used				
Dobutamine	434 (81)	92 (82)	342 (81)	0.76
Norepinephrine	254 (47)	45 (40)	209 (49)	0.08
Epinephrine	54 (10)	6 (5)	48 (11)	0.06
Levosimendan	41 (8)	5 (4)	36 (9)	0.15
Isoprenaline	26 (5)	1 (1)	25 (6)	0.03
Organ replacement therapies				
Respiratory support				
Invasive	182 (34)	38 (34)	144 (34)	0.98
Noninvasive	132 (25)	14 (13)	118 (28)	<0.001
Mechanical circulatory support				
Intra-aortic balloon pump	31 (6)	10 (9)	21 (5)	0.10
Impella	13 (2)	6 (5)	7 (2)	0.02
Extracorporeal membrane oxygenation	43 (8)	5 (5)	38 (9)	0.12
Length of intensive care unit stay	17 (11–28)	17 (13–26)	17 (11–28)	0.80
Length of hospital stay	11 (7–20)	11 (7–16)	12 (7–21)	0.15
Renal replacement therapy	48 (9)	4 (4)	44 (10)	0.02
LVEF at discharge, % (n=432)	35±14	29±11	37±15	<0.001
LVEF ≤50%	368/432 (85)	97/102 (95)	271/330 (82)	0.001
LVEF improvement from admission	9±14	7±10	9±15	0.34

New York Heart Association classification at discharge (n=338)				0.72
1	73/338 (22)	13/76 (17)	60/262 (23)	
2	162/338 (48)	39/76 (51)	123/262 (47)	
3	83/338 (25)	20/76 (26)	63/262 (24)	
4	20/338 (6)	4/76 (5)	16/262 (6)	
Medications at discharge				
Aspirin	314 (59)	73 (65)	241 (57)	0.12
P2Y12 inhibitors	166 (31)	45 (40)	121 (29)	0.02
Statins	293 (55)	73 (65)	220 (52)	0.01
Beta blockers	303 (57)	112 (100)	191 (45)	<0.001

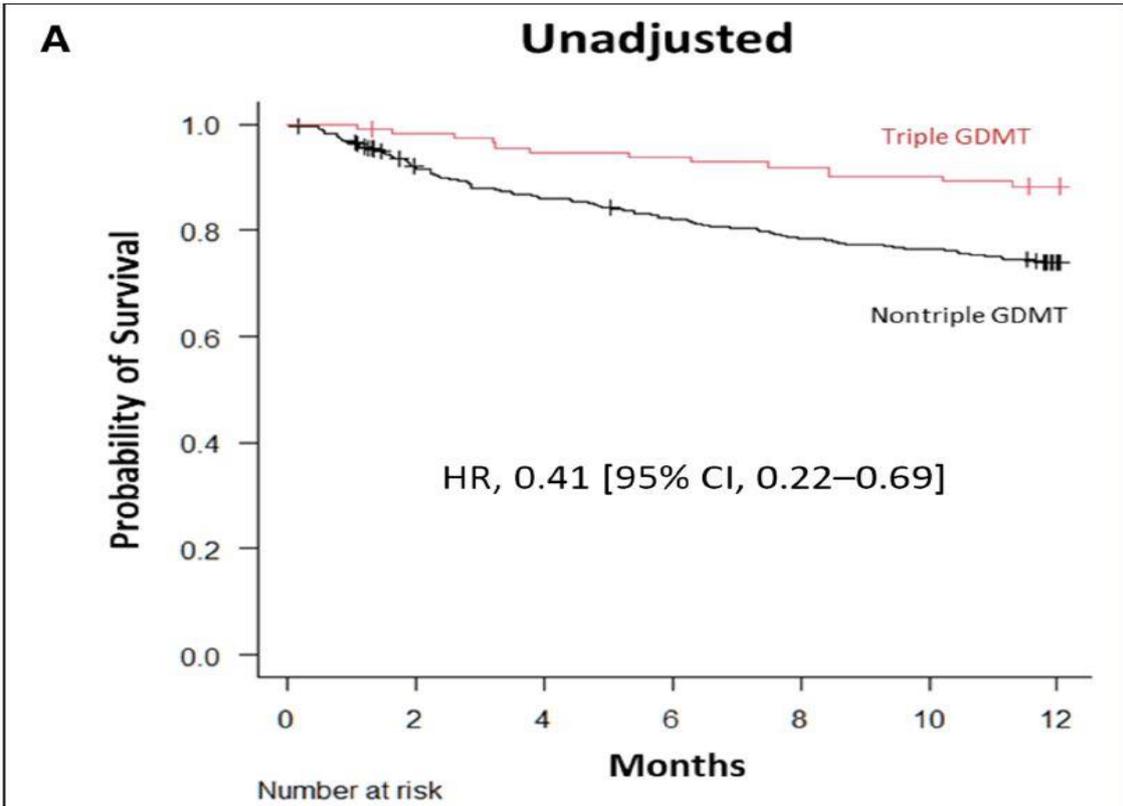
	Overall population (n=535)	Triple GDMT (n=112)	Nontriple GDMT (n=423)	P value
Vitamin K antagonist	152 (28)	32 (29)	120 (28)	0.97
Direct oral anticoagulants	64 (12)	25 (22)	39 (9)	<0.001
Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers	339 (63)	107 (96)	232 (55)	<0.001
Sacubitril/valsartan	17 (3)	6 (5)	11 (3)	0.14
Loop diuretics	337 (63)	86 (77)	251 (59)	<0.001
Aldosterone antagonist	169 (32)	112 (100)	57 (13)	<0.001
Amiodarone	138/527 (26)	30/111 (27)	108/416 (26)	0.82
Proton pump inhibitor	349/524 (67)	78/109 (72)	271/415 (65)	0.22
Destination after discharge				0.03
Transferred to other hospital	197/424 (46)	38/86 (44)	159/338 (47)	
Home	169/424 (40)	43/86 (50)	126/338 (37)	
Convalescence center	42/424 (10)	5/86 (6)	37/338 (11)	
Others	16/424 (4)	0/86 (0)	16/338 (5)	

Values are n (%) or n/N (%), or mean±SD. GDMT indicates guideline-derived medical therapy; and LVEF, left ventricular ejection fraction.

**Table 3.** One-Year Clinical Outcomes (Table view)

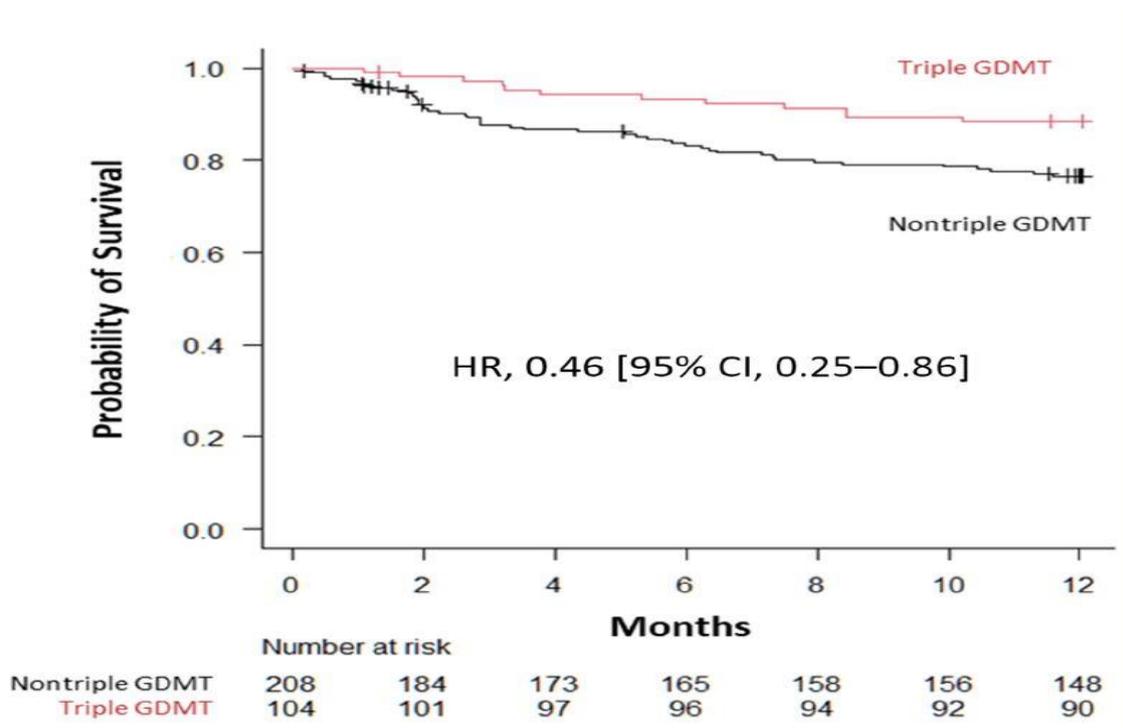
	Overall population (n=523)	Triple GDMT (n=111)	Nontriple GDMT (n=412)	P value
Death	121 (23)	13 (12)	108 (26)	0.001
Unplanned cardiovascular rehospitalization	281/450 (63)	64/93 (69)	217/357 (61)	0.15
Heart transplantation	33 (6)	2 (2)	31 (8)	0.03
Left ventricular assist device or biventricular assist device	33 (6)	7 (6)	26 (6)	1.00

Values are n (%) or n/N (%). GDMT indicates guideline-derived medical therapy.

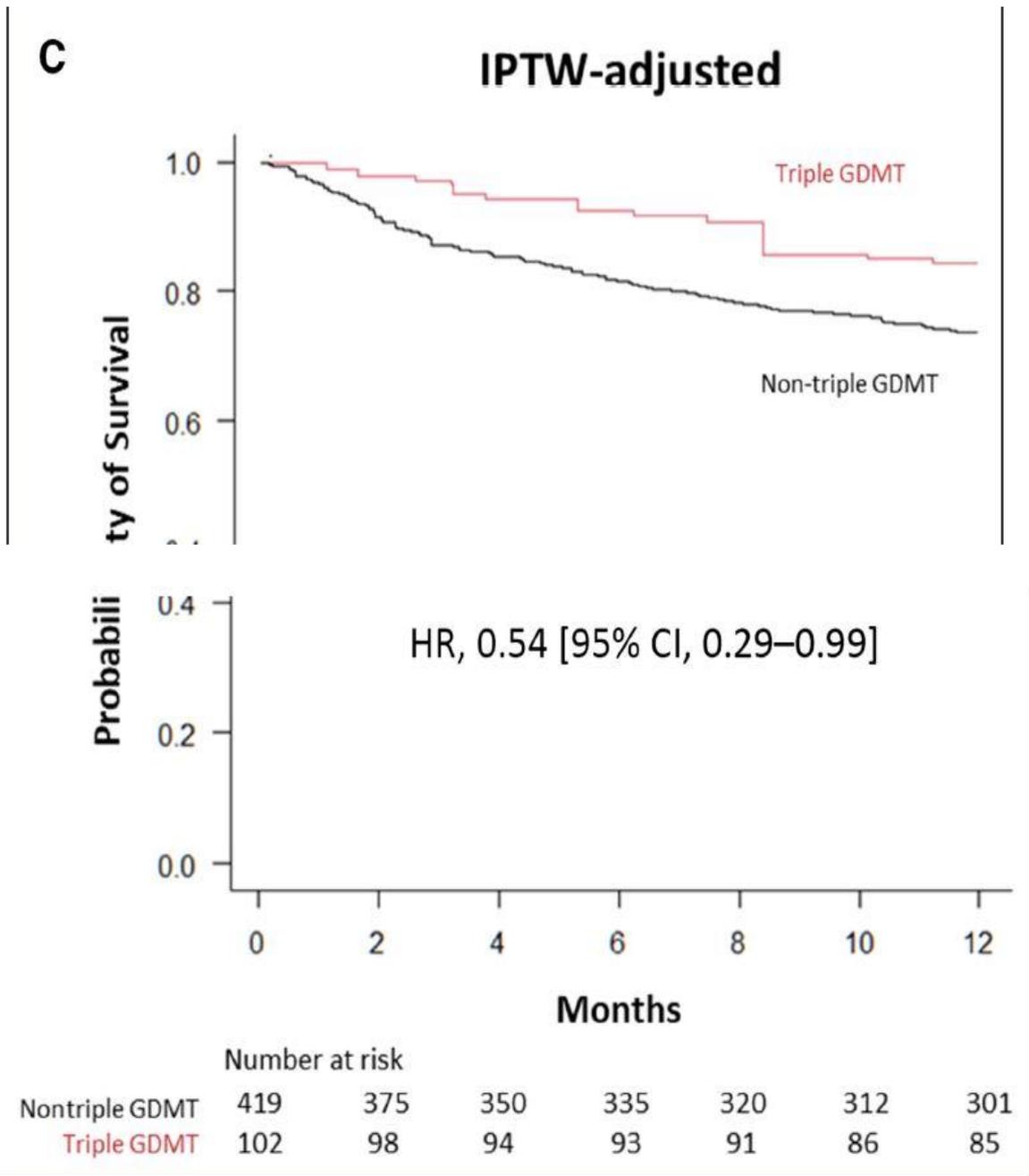


Nontriple GDMT	423	380	355	338	323	314	295
Triple GDMT	112	109	105	104	102	100	97

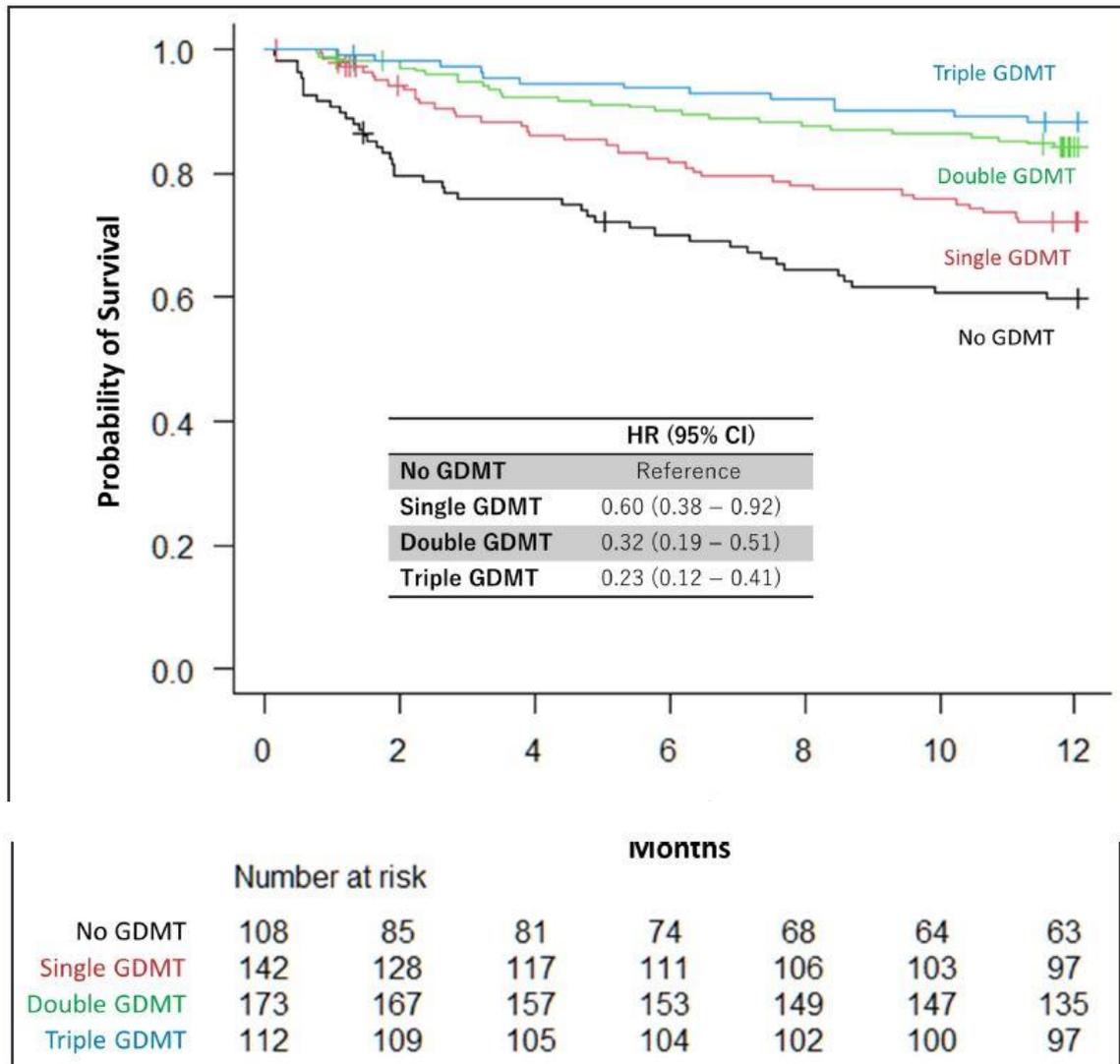
### B 2:1 propensity matched cohort



Nontriple GDMT	208	184	173	165	158	156	148
Triple GDMT	104	101	97	96	94	92	90



**Figure 2.** Relationship between triple GDMT and all-cause mortality in patients who were successfully discharged after cardiogenic shock. Kaplan–Meier curves indicate the incidence rate of all-cause mortality: (A) unadjusted, (B) 2:1 propensity match, and (C) inverse probability of treatment weighting (IPTW) adjusted. GDMT, guideline-derived medical therapy; and HR, hazard ratio.



**Figure 3.** Kaplan–Meier curves according to the number of heart failure drugs at discharge. GDMT indicates guideline-derived medical therapy; and HR, hazard ratio.

### Predictors of 1-Year Mortality in Patients With Cardiogenic Shock

The univariate Cox regression analysis indicated that age, dyslipidemia, prior implantable cardioverter-defibrillator, prior percutaneous coronary intervention, stroke history, chronic renal failure, chronic obstructive pulmonary disease, active cancer, estimated glomerular filtration rate, in hospital percutaneous coronary intervention, LVEF at discharge, aspirin, P2Y12 inhibitors, statins, loop diuretics, and triple GDMT at discharge were significant predictors of mortality at 1 year (Table S6). Contrary to our prior report, which focused on 30-day outcomes,<sup>3</sup> increased lactate level was not associated with mortality in survivors of CS at 1-year follow-up. In the first model of multivariate analysis, age (per year: HR, 1.03 [95% CI, 1.01–1.05],  $P=0.002$ ), active cancer (HR, 2.39 [95% CI, 1.00–4.98],  $P=0.02$ ), LVEF at discharge (per %: HR, 0.98 [95% CI, 0.96–1.00],  $P=0.02$ ), and triple GDMT at discharge (HR, 0.44 [95% CI, 0.19–0.80],  $P=0.007$ ) were independent predictors of 1-year all-cause mortality (Table 4). Another multivariate model was made to examine whether the number of HF drugs was associated with the outcome of patients (Table 4). In this model, the number of

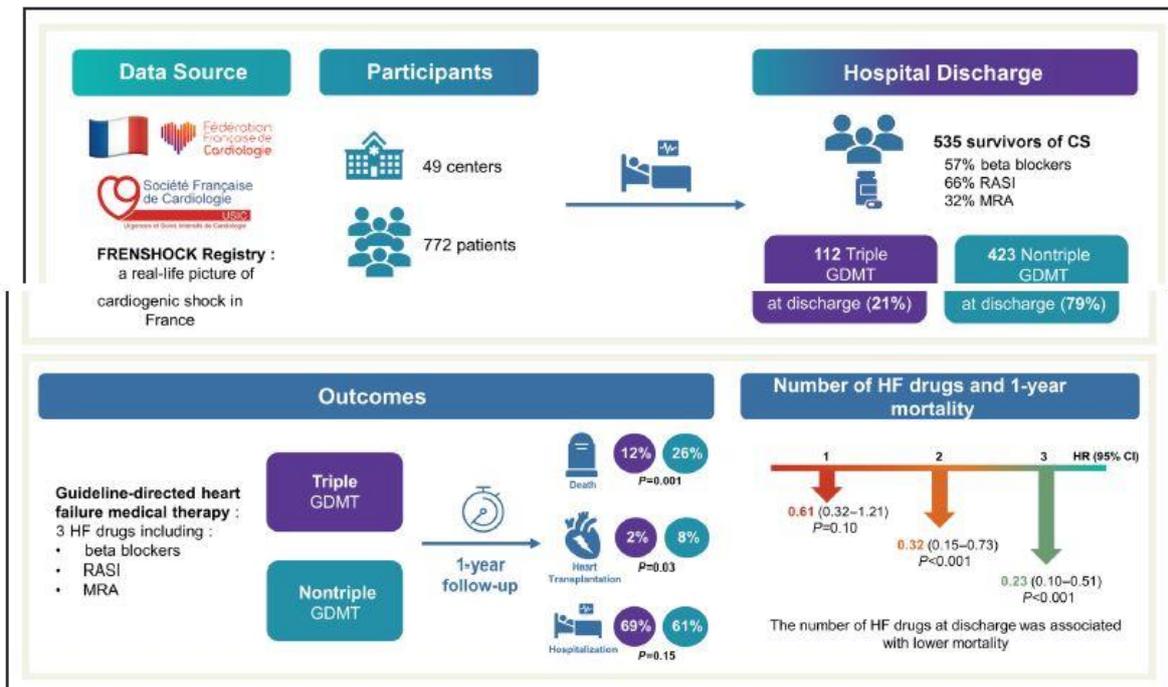
HF drugs at discharge was included in the model instead of triple GDMT. Consequently, the number of HF drugs at discharge was negatively associated with 1-year all-cause mortality (Table 4 and Figure 4). Two additional multivariate analysis models, incorporating confounding factors based on existing knowledge, were performed and yielded consistent results (Table S7). Cox assumptions of those analyses are indicated in Table S8 and linear assumptions of continuous values are shown in Figure S3. In contrast, the number of HF drugs on admission was not an independent factor of 1-year mortality (Tables S9 and S10). The impact of diuretics at discharge on mortality was assessed using Kaplan–Meier curves in patients with and without triple GDMT at discharge (Figure S4). Diuretics at discharge were associated with worse outcomes, probably reflecting the congestive state of the patients.

**Table 4.** Univariate and Multivariate Cox Regression Analyses for Prediction of 1-Year Mortality (Table view)

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
<b>Model 1</b>				
Age (an increase of 1 y old)	1.03 (1.02–1.05)	<0.001	1.03 (1.01–1.05)	0.002
Dyslipidemia	1.58 (1.10–2.23)	0.01	1.40 (0.87–2.29)	0.16
Defibrillator	1.57 (1.01–2.41)	0.047	1.36 (0.68–2.50)	0.29
Prior PCI	1.77 (1.10–2.57)	0.006	0.96 (0.48–1.72)	0.87
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Stroke history	2.11 (1.05–3.57)	0.02	1.57 (0.59–3.54)	0.23
Chronic renal failure	2.05 (1.38–2.93)	<0.001	1.06 (0.54–1.84)	0.84
Chronic obstructive pulmonary disease	2.35 (1.21–3.86)	0.005	1.94 (0.77–4.15)	0.06
Active cancer	2.84 (1.46–4.37)	<0.001	2.39 (1.00–4.98)	0.02
PCI to culprit lesion	0.48 (0.28–0.71)	<0.001	0.54 (0.24–1.22)	0.10
LVEF at discharge (an absolute increase of 1%)	0.98 (0.96–0.99)	0.003	0.98 (0.96–1.00)	0.02
Aspirin at discharge	0.57 (0.40–0.81)	0.002	0.64 (0.37–1.16)	0.09
P2Y12 inhibitors at discharge	0.63 (0.40–0.94)	0.03	1.18 (0.59–2.30)	0.61
Statins at discharge	0.63 (0.44–0.91)	0.01	0.94 (0.53–1.68)	0.82
Loop diuretics at discharge	1.83 (1.22–2.86)	0.003	1.16 (0.57–2.31)	0.59
Triple GDMT at discharge	0.41 (0.21–0.69)	<0.001	0.44 (0.19–0.80)	0.007
<b>Model 2</b>				
Age (an increase of 1 y old)	1.03 (1.02–1.05)	<0.001	1.03 (1.01–1.05)	0.002
Dyslipidemia	1.58 (1.10–2.23)	0.01	1.53 (0.89–2.48)	0.07
Defibrillator	1.57 (1.01–2.41)	0.047	1.17 (0.59–2.27)	0.60
Prior PCI	1.77 (1.10–2.57)	0.006	1.13 (0.60–2.17)	0.66
Stroke history	2.11 (1.05–3.57)	0.02	1.27 (0.39–2.99)	0.52
Chronic renal failure	2.05 (1.38–2.93)	<0.001	1.17 (0.61–2.22)	0.57
Chronic obstructive pulmonary disease	2.35 (1.21–3.86)	0.005	2.09 (0.78–4.51)	0.04
Active cancer	2.84 (1.46–4.37)	<0.001	1.94 (0.80–4.29)	0.09
PCI to culprit lesion	0.48 (0.28–0.71)	<0.001	0.70 (0.28–1.70)	0.36
LVEF at discharge (an absolute increase of 1%)	0.98 (0.96–0.99)	0.003	0.97 (0.95–1.00)	0.003
Aspirin at discharge	0.57 (0.40–0.81)	0.002	0.63 (0.34–1.12)	0.08
P2Y12 inhibitors at discharge	0.63 (0.40–0.94)	0.03	1.03 (0.48–2.15)	0.92
Statins at discharge	0.63 (0.44–0.91)	0.01	1.03 (0.58–2.03)	0.93
Loop diuretics at discharge	1.83 (1.22–2.86)	0.003	1.32 (0.66–2.54)	0.32

Numbers of heart failure drugs at discharge				
0	Reference	...	Reference	...
1	0.60 (0.38–0.96)	0.02	0.61 (0.32–1.21)	0.10
2	0.32 (0.19–0.52)	<0.001	0.32 (0.15–0.73)	<0.001
3	0.23 (0.12–0.41)	<0.001	0.23 (0.10–0.51)	<0.001

GDMT indicates guideline-derived medical therapy; LVEF, left ventricular ejection fraction; LVEF, left ventricular ejection fraction; and PCI, percutaneous coronary intervention.



**Figure 4.** Incidences and clinical outcomes of patients receiving guideline-directed medical therapy for heart failure following cardiogenic shock.

CS indicates cardiogenic shock; GDMT, guideline-derived medical therapy; FRENDSHOCK, French Observatory on the Management of Cardiogenic Shock in 2016; HF, heart failure; HR, hazard ratio; MRA, mineralocorticoid receptor antagonists; and RASI, renin-angiotensin system inhibitors.

## Sensitivity Analyses Using Propensity Score Models

Sensitivity analyses using propensity score models were performed to confirm this study's findings. The patient characteristics and the standardized difference of the 2:1 propensity score-matched cohort are shown in Table S11. Despite a smaller number of patients (n=312), the positive effect of triple GDMT at discharge remained significant (HR, 0.46 [95% CI, 0.24–0.86],  $P=0.02$ ) (Figure 2B). Likewise, the inverted probability of treatment weighting analysis consistently found that triple GDMT at discharge was significantly associated with lower 1-year mortality (HR, 0.54 [95% CI, 0.29–0.99],  $P=0.047$ ) (Table S12 and Figure 2C). The distributions of propensity scores and weights are indicated in Figure S5. Doubly robust analysis consistently showed a lower 1-year mortality rate in patients with triple GDMT at discharge (HR 0.48 [95% CI, 0.25–0.94],  $P=0.03$ ).

## DISCUSSION

We investigated the clinical impact of triple GDMT in patients post-CS from a prospective, largescale, multicenter registry. The current analysis revealed the following salient findings: (1) the rate of triple GDMT prescription at discharge was relatively low in patients post-CS (21% of the whole cohort); (2) patients with lower LVEF were likely to receive triple GDMT at discharge; and (3) triple GDMT at discharge was associated with better survival at 1 year after CS events.

CS remains a strong predictor of mortality in patients with acute HF. Although systolic dysfunction subsequent to acute MI (the major cause of ischemic CS) has been the classical cause of CS,<sup>5</sup> a recent large registry from North America, which enrolled 3049 patients from cardiac intensive care units between 2017 and 2018, indicated that acute MI was responsible for less than one-third of all patients with CS.<sup>18</sup> This striking evolution may have been influenced by the recent declining incidence of ST-segment–elevation MI probably due to the improvement of anti-atherosclerosis drugs and the global increase in the number of patients with HF.<sup>18</sup> Consistently, in our population, nonischemic CS was found in more than half of the patients, which may also reflect the broader selection of patients from intensive cardiac care units, intensive care units, and emergency departments.<sup>3</sup>

Although an improvement in survival has been observed in both ischemic and nonischemic CS,<sup>3, 19</sup> recent registries demonstrated that in-hospital mortality rates of patients with CS remain to be approximately 20% to 30%.<sup>3, 12, 19</sup> Given the high in-hospital mortality rate of patients with CS,<sup>20</sup> the management of CS has been centered on in-hospital treatments that include coronary revascularization, intensive care measures, and mechanical circulatory support.<sup>5, 21, 22, 23</sup> Although there is no solid supporting evidence regarding post-CS medical therapy, the choice of discharge medication has been based on current heart failure and myocardial infarction guidelines.<sup>6, 24, 25</sup> Triple GDMT drugs consisting of beta blockers, RASI, and MRA are commonly recommended in those guidelines, particularly in patients with reduced left ventricular systolic function.<sup>6, 24</sup> In the present study, lower LVEF levels were found in the triple GDMT group, suggesting that the attending physicians were likely to select multiple HF drugs for patients with low LVEF at discharge.

Although an improvement of LVEF after CS can be observed in a considerable number of patients following coronary revascularization, recovery from severe inflammation, volume optimization, and introduction of HF drugs, adverse clinical events may occur as a consequence of adverse cardiac remodeling, residual ischemia, incomplete LVEF recovery, or progression of the baseline diseases,<sup>6, 24, 25, 26</sup> which all can be targeted by beta blockers, RASI, and MRA, which compose the triple GDMT.<sup>6, 24, 27</sup> Although there has been no randomized clinical trial that investigated the effects of HF drugs at the recovery phase of patients with CS, the recent STRONG-HF (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies) trial demonstrated that rapid titration of GDMT using beta blockers, RASI, and MRA reduced the risk of 180-day all-cause death or HF hospitalization in patients with acute HF without shock. In addition, improved blood pressure, pulse, New York Heart Association class, body weight, and NT-proBNP (N-terminal pro-brain natriuretic peptide) concentration were found in patients with GDMT, indicating the beneficial effects of these drugs not only on hard end points but also on symptoms and quality of life.<sup>28</sup> Moreover, TRED-HF (Therapy Withdrawal in Recovered Dilated Cardiomyopathy-Heart Failure) trial was the first randomized trial to demonstrate the effect of HF drugs, consisting of beta blockers, RASI, and MRA, in patients deemed to have

recovered dilated cardiomyopathy, reinforcing the importance of continuous HF treatments even after LVEF recovery.<sup>29</sup> This trial revealed that withdrawal of HF drugs was associated with relapse of nonischemic dilated cardiomyopathy within 6 months, suggesting that improvement in cardiac function following treatment does not reflect full and sustained recovery but rather reflects remission, which requires continuous treatments. Although further investigations are required in patients with improved LVEF secondary to ischemic heart disease, RASI and beta blockers have the potential to reduce further coronary events as well as morbidity and mortality related to HF. Thus, given the high-risk profile of patients with CS, it is justifiable to extrapolate that HF drugs prevent future cardiac events regardless of the triggers. Our data support the notion that patients who recovered from severe LVEF impairment are likely to benefit from early introduction of long-term pharmacological HF treatments.

Concordant with prior reports, older age and impaired renal function were the factors of underuse of GDMT, indicating that perceived frailty and comorbidities may have been partly responsible for the drug selection.<sup>30</sup> However, elderly patients without signs of fragility or drug intolerance may benefit from GDMT and therefore, current guidelines recommend the initiation of GDMT during hospitalization without any age limit.<sup>30, 31</sup> Moreover, it has been reported that spironolactone and beta blockers might be rather protective in patients with HF with worsening renal function, whereas no negative effects have been evidenced with RASI in those patients.<sup>32</sup> Thus, it is now indicated in the guidelines that physicians should be aware that true contraindications of GDMT are rare, such as the acute phase of CS that may preclude the use of certain medications until resolution of shock state, advanced degree atrioventricular block for beta blockers in the absence of pacemakers, or angioedema for RASI.<sup>31</sup> Given the evidence that almost half of patients with HF with reduced EF have no change made to oral HF drugs in the 12 months after discharge,<sup>33</sup> it could be pertinent to initiate and optimize GDMT during hospitalization.

Whereas the in-hospital mortality in patients with CS has shown a mild reduction in recent years,<sup>20</sup> our data evidenced that the mortality rate of survivors from CS at 1 year was 23%, indicating that the high-risk profile persists even after the recovery from the acute phase. The NCDR ACTION Registry-GWTG (National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network-Get With the Guidelines) was a large registry that enrolled 112 668 survivors of acute MI between 2007 and 2012.<sup>2</sup> Similar to our study, the 1-year mortality rate was 22.4% among the patients who experienced CS during hospitalization. Moreover, HF hospitalization occurred in 32.5% of the patients with CS, suggesting a chronic HF phenotype in patients post-CS. The persistent high-risk profile might be attributed, in part, to persistent impaired cardiac function, residual ischemia, cardiac fibrosis, arrhythmia—all of which can be addressed through triple GDMT.

Furthermore, hospitalized patients would encounter deconditioning, malnutrition, and sleep disturbance, all of which can negatively affect post-discharge prognosis. Considering that patients with CS are in a more critical condition and experience longer hospitalizations compared with those without CS, these individuals would be more vulnerable to these factors. Although conflicting results have been reported regarding the prognosis in ischemic and nonischemic CS,<sup>10, 12, 18, 19</sup> the 1-year mortality rate in the present study was similar between the 2 triggers, indicating that the high-risk profile can be found in patients post-CS regardless of CS phenotypes. Although the underlying causes of the equivalent results in the 2 triggers lie beyond the scope of the present study, we assume that they may have been influenced by the improved prognosis of patients with ST segment–elevation MI over the past few decades and the diverse range of patients included, not only from intensive cardiac care

units but also from general intensive care units. Previously, we identified that an infectious trigger was an independent factor of early mortality, likely leading to mixed shock that necessitates norepinephrine and renal replacement therapy.<sup>3</sup> In the present study, patients with nonischemic CS had a higher likelihood of experiencing infectious disease (12% versus 4%,  $P=0.003$ ) and were associated with an extended duration of hospitalization (18 days versus 15 days,  $P=0.02$ ), which may have played a role in exacerbating the adverse clinical outcomes observed in these patients.

To the best of our knowledge, this is the first study to examine the beneficial effects of HF drugs in survivors of CS. Given the high mortality rate and low prescription rate of triple GDMT in survivors of CS, our study emphasizes the importance of optimizing pharmacological therapy to improve survival rate of patients post-CS.

### **Future Perspectives**

Most recently, clinical trials have highlighted the cardiorenal protective effects of SGLT2 inhibitors in both patients with HF with reduced EF and HF with preserved EF regardless of their diabetes status.<sup>34, 35</sup> The underlying mechanisms have been partly elucidated by clinical and preclinical studies including ours, demonstrating the cardioprotective effects of SGLT2 inhibitors on left ventricular fibrosis and diastolic dysfunction, pulmonary artery remodeling, coronary microvascular disorder, endothelial dysfunction, inflammation, and oxidative stress.<sup>36, 37</sup> In the latest European Society of Cardiology guidelines, these drugs are now considered an evidence-based oral medication for patients with chronic HF. Nevertheless, future studies are warranted to investigate the impact of SGLT2 inhibitors and the combination of the 4 new GDMT drugs on patients with post-CS.

### **Study Limitations**

We acknowledge the following limitations: First, this was an observational study, and no sample size calculation was performed. However, in general, randomized clinical trials in CS are difficult to perform with an adequate number of patients. Thus, real-world registries are an important source to explore optimal medical treatments. Second, this retrospective analysis of FRENDSOCK lacked information on the achieved up-titrated drug doses during follow-up. Moreover, a noteworthy limitation arises from the inclusion of time-varying covariates, particularly the changes in treatment observed post-discharge. This aspect of our data introduces complexity, potentially influencing the robustness of our findings. Third, underlying comorbidities such as chronic obstructive pulmonary disease, chronic kidney disease, hyperkalemia, and side effects may have influenced the initiation of the HF drugs. However, those factors did not show any difference between the 2 treatment groups or were adjusted in the multivariate analyses. Fourth, although blood pressure after achieving clinical stability may have also influenced the drug initiation, those data were not collected in the current study. Nevertheless, numerous studies have reported the benefits of GDMT irrespective of blood pressure.<sup>38, 39</sup> Fifth, the clinical data of rehospitalization include any types of unplanned cardiovascular hospitalization following CS and was not dedicated to HF events. Patients who died within 1 year were likely to have less hospitalization perhaps due to the shorter duration of follow-up, suggesting that the hospitalization rate may have been underestimated in the non-triple GDMT group. Moreover, the data should be interpreted with caution because of the incomplete follow-up rate (86%). Sixth, LVEF was not evaluated during the follow-up phase. Therefore, the improvement/relapse of HF at the chronic phase remains uncertain. Seventh, GDMT may not favor certain CS phenotypes such as right

ventricular infarction or pulmonary hypertension, which are not associated with the deterioration in LVEF. Further investigations are needed to identify specific pathological conditions which benefit from triple GDMT. Eighth, Society for Cardiovascular Angiography & Interventions SHOCK Stage Classification<sup>40</sup> was not used for the group classification, given that this score was not yet available at the time of the study. Ninth, baseline HF phenotypes and LVEF before the CS events were unavailable in our registry. Consequently, we were unable to ascertain the specific pathological conditions that respond to GDMT following CS. Finally, although we attempted to assess the relationship between CS and post-hospital outcomes by adjusting for a broad range of clinical factors and treatments, the possibility of confounding by unmeasured covariates remains. However, in the propensity score matched and inverted probability of treatment weighting analyses, there was substantial overlap among estimated propensity scores, suggesting that the positivity assumption required was met. Our data contained minimal amounts of missing data, and the multiple imputation techniques demonstrated high consistency in the estimated propensity scores, allowing us to combine the imputed results for a comprehensive analysis.

## CONCLUSIONS

The current study reveals that hospital survivors of CS are vulnerable to adverse outcomes during the follow-up phase. The concomitant administration of beta blockers, RASI, and MRA in the convalescence phase of patients with CS is associated with better 1-year survival. This finding indicates that survivors of CS require optimal HF treatments to address the vulnerable post-hospital period.

## SOURCES OF FUNDING

The study was sponsored by the Fédération Française de Cardiologie and was funded by unrestricted grants from Daiichi-Sankyo and Maquet SAS. Complementary grants will be sought for dedicated research projects within the main study.

## ACKNOWLEDGMENTS

FRENDSHOCK is a registry of the French Society of Cardiology, managed by its Emergency and Acute Cardiovascular Care Working Group. Our thanks go to all the devoted personnel of Société Française de Cardiologie who participate in the upkeep of the registry. The authors are deeply indebted to all the physicians who took care of the patients at the participating institutions.

## DISCLOSURES

None.

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