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Current use of inotropes according to initial blood pressure and peripheral perfusion in the treatment of congestive heart failure: findings from a multicentre observational study

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ABSTRACT

Objectives Current guidelines restrict the use of inotropes for the treatment for heart failure (HF) unless the patients are hypotensive or hypoperfused because of safety concerns. This study sought to characterise the contemporary real-world use of inotropes and associated long-term outcomes according to systolic blood pressure (sBP) and perfusion status.

Design A multicentre prospective cohort study.

Setting This study was nested from the Kyoto Congestive Heart Failure registry, which included consecutive Japanese patients admitted for HF.

Participants We categorised 3995 patients into two groups: sBP ≥90 mm Hg and warm profile group, and sBP <90 mm Hg or cold profile group. In each group, patients were stratified across the use of inotropes within 24 hours of hospital presentation.

Primary and secondary outcomes The primary outcome was all-cause death throughout follow-up. Secondary outcomes included cardiovascular death throughout follow-up, all-cause death during index hospitalisation and after discharge, and HF hospitalisation.

Results A total of 793 patients (20%) presented with sBP <90 mm Hg or cold profile, whereas 3202 patients had sBP ≥90 mm Hg and warm profile; 276 patients (35%) in the sBP <90 mm Hg/cold group and 312 patients (10%) in the sBP ≥90 mm Hg/warm group received initial inotropic treatment. Adjusted excess risk of inotrope use relative to no inotrope for the primary outcome measure was significant in the sBP ≥90 mm Hg/warm group (adjusted HR), 1.36; 95% CI 1.09 to 1.72, p=0.006) but not in the sBP <90 mm Hg/cold group (adjusted HR, 1.28, 95% CI 0.96 to 1.69, p=0.09). Risk for postdischarge all-cause death and HF hospitalisation was not significantly different between the patients with inotropes and no inotropes in both groups.

Conclusion Inotrope use in the absence of hypotension and hypoperfusion is still common, but associated with a worse long-term prognosis.

Trial registration number UMIN000015238.

Strengths and limitations of this study

- ► This study offers the current real-world patterns and outcomes of initial inotropic treatments in congestive heart failure.
- ► Data are derived from a large contemporary cohort in Japan.
- ► The observational nature of this study precludes the demonstration of a causal relationship between initial inotrope use and outcomes.
- ► Despite a careful and comprehensive attempt to correct the heterogeneity of the patient characteristics, unmeasured covariates may account for outcomes.
- ► The exact dose of inotropic agents and duration of their use were not available.

INTRODUCTION

Congestive heart failure (HF) is a life-threatening medical condition that often requires in-hospital management. Most hospitalised patients with HF are treated with diuretics to attenuate fluid overload, while others may receive intravenous vasodilators, which decrease ventricular filling pressure and relieve symptoms.[1–5] On the other hand, inotropes can be used for patients with a severe reduction in cardiac output to maintain vital

organ perfusion and blood pressure. However, previous studies have raised concerns regarding safety of inotrope use due to increased morbidity and mortality.[6–8] Inotropes, especially those with adrenergic mechanisms such as dobutamine and dopamine, can increase left ventricular afterload and cause tachycardia, myocardial ischaemia and arrhythmias. Non-catecholamine inotropes, such as milrinone, may increase the risk of hypotension.[9] Thus, current American College of Cardiology (ACC)/American Heart Association (AHA) guideline states that the use of intravenous inotropic agents in hospitalised patients without documented low blood pressure or impaired perfusion is potentially harmful (Recommendation: class III, level of evidence: B).[2] Current European Society of Cardiology (ESC) guideline also limits the use of inotropes to the patients with hypotension or to those with signs of impaired peripheral perfusion such as 'cold' HF profile (Recommendation: class III, level of evidence: A).[1] However, decisions regarding the initial use of vasoactive agents still remains largely subject to clinician discretion.[1 2 4] Despite an important decision making basis for the initiation of inotropes, few studies have considered the clinical signs of perfusion status such as the 'cold' or 'warm' profile for the evaluation of outcomes.[10] In addition, most previous studies have evaluated the short-term morbidity and mortality of inotrope use, but data on long-term outcomes associating inotrope use are scarce.[10]

The aim of this study is to assess the current initial use of inotropic therapy and associated outcomes according to initial blood pressure and perfusion status in contemporary real-world practice in Japan.

METHODS

Patient population

The Kyoto Congestive Heart Failure (KCHF) registry is a physician-initiated, prospective, observational, multicentre cohort study that enrolled, without exclusion, all consecutive patients who were hospitalised for congestive HF between October 2014 and March 2016 in 19 participating hospitals in Japan. All patients enrolled in the KCHF registry had signs and symptoms of HF defined by modified Framingham criteria[11 12] and required intravenous drugs within 24 hours of hospital presentation. For those patients with repeated HF hospitalisation during the study period, the first HF hospitalisation was selected as an index hospitalisation. The overall design of the KCHF study has been described in detail.[13–15]

All study procedures were conducted in compliance with the ethical principles of the Declaration of Helsinki. Clinical follow-up data were collected from hospital medical records or by contact with patients, their relatives or their referring physicians in October 2017.[16]

Definitions

Inotrope use was defined as treatment with dopamine, dobutamine or phosphodiesterase inhibitors within 24 hours of hospital presentation. Norepinephrine was categorised as a vasopressor. Levosimendan was not available in Japan and was not included in this study. According to the systolic blood pressure (sBP) and data on the HF profile including 'warm' (ie, adequately perfused) and 'cold' (hypoperfused) on presentation, we stratified all patients into two groups: sBP ≥90 mm Hg/warm group, and sBP <90 mm Hg/cold group.

Outcomes

The primary outcome was all-cause death throughout a 1-year follow-up. Secondary outcomes included all-cause death during index hospitalisation and all-cause death after discharge, cardiovascular death throughout the 1-year follow-up, and HF hospitalisation. The causes of death were classified according to the Valve Academic Research Consortium definitions and adjudicated by a clinical event committee.[17]

Statistical analysis

Categorical variables are expressed as numbers and percentages and are compared using the χ^2 test. Continuous variables are expressed as means with SD or medians with IQRs and are compared using an analysis of variance or the Kruska-Wallis test depending on their distributions. The cumulative incidences of the primary and secondary outcome measures, except for all-cause death during hospitalisation, were estimated by the Kaplan-Meier method and compared using the log-rank test. We estimated HRs and 95% CIs with Cox's proportional hazards regression models. Proportional hazard assumptions for risk-adjusting variables were assessed on the plots of log (time) vs log [−log (survival)] stratified by the variable, and verified to be acceptable. In the Cox's proportional hazards model, we simultaneously included the clinically relevant factors listed in table 1 as risk-adjusting variables and incorporated the centres as stratification variables. The risk for all-cause death during hospitalisation was assessed by a logistic regression model in which we constructed parsimonious models with the 11 clinically most relevant risk-adjusting variables listed in table 1 because of a small number of patients with outcome. Analyses of Cox's proportional hazards model with stratification were performed with SPSS V.19 (IBM). All other analyses were performed with JMP V.12.01 software (SAS Institute) and GraphPad Prism V.6.05 (GraphPad Software, La Jolla, California, USA). In this study, all reported p values were two tailed, and $p<0.05$ was considered to be significant.

Patient and public involvement

Patients or the public were not involved in the design, conduction, or reporting, or in the dissemination plans of our research.

RESULTS

Clinical characteristics

Among 3995 patients in this study (median age, 80 years; 1786 (45%) women), 121 (3%) had a sBP <90 mm Hg,

Table 1 Characteristics of the patients with inotrope use and no inotrope use according to sBP and perfusion profile

	sBP ≥90 mm Hg and warm, N=3202			sBP <90 mm Hg or cold, N=793		
	No inotrope use, n=2890	Inotrope use, n=312	P value	No inotrope use, n=517	Inotrope use, n=276	P value
Clinical characteristics						
Age, years	81 (73–86)	81 (71–87)	0.53	79 (68–86)	78 (67–85)	0.17
Age ≥80 years*†	1570 (54)	168 (54)	0.87	253 (49)	122 (44)	0.2
Female*†	1354 (47)	128 (41)	0.05	213 (41)	91 (33)	0.02
BMI, kg/m^2	23.0±4.5	22.2±4.4	<0.001	22.6±4.3	22.0±4.3	0.08
BMI <22 kg/m^2*†	1236 (43)	154 (49)	0.026	234 (45)	137 (50)	0.24
Aetiology						
Ischaemic	875 (30)	122 (39)	0.001	187 (36)	125 (45)	0.01
ACS*†	120 (4)	23 (7)	0.009	53 (10)	37 (13)	0.18
Cardiomyopathy	346 (12)	72 (23)	<0.001	97 (19)	82 (30)	<0.001
Valvular	611 (21)	64 (21)	0.8	98 (19)	35 (13)	0.02
Medical history						
Prior hospitalisation for HF*†	954 (33)	127 (41)	0.006	206 (40)	126 (46)	0.11
Atrial fibrillation or flutter*†	1285 (44)	98 (31)	<0.001	193 (37)	85 (31)	0.07
Hypertension*†	2166 (75)	192 (62)	<0.001	365 (71)	147 (53)	<0.001
Diabetes mellitus*	1059 (37)	117 (38)	0.77	194 (38)	121 (44)	0.08
Dyslipidaemia	1129 (39)	113 (36)	0.33	183 (35)	104 (38)	0.52
Prior myocardial infarction*	621 (21)	89 (29)	0.005	117 (23)	71 (26)	0.33
Prior stroke*	486 (17)	53 (17)	0.94	70 (14)	43 (16)	0.43
Prior PCI or CABG	722 (25)	82 (26)	0.62	120 (23)	79 (29)	0.09
Current smoking*	315 (11)	32 (10)	0.73	90 (17)	31 (11)	0.02
Ventricular tachycardia/fibrillation	74 (3)	23 (7)	<0.001	36 (7)	31 (11)	0.04
Chronic kidney disease	1260 (44)	151 (48)	0.1	231 (45)	137 (50)	0.18
Chronic lung disease*	395 (14)	40 (13)	0.68	61 (12)	33 (12)	0.95
Malignancy	435 (15)	48 (15)	0.88	60 (12)	30 (11)	0.8
Dementia	524 (18)	72 (23)	0.03	106 (21)	55 (20)	0.8
Social backgrounds						
Poor medical adherence	483 (17)	52 (17)	0.98	87 (17)	44 (16)	0.65
Living alone*	611 (21)	61 (20)	0.51	116 (22)	63 (23)	0.9
With occupation	335 (12)	51 (16)	0.01	77 (15)	40 (14)	0.88

Continued

Table 1 Continued

	sBP ≥90 mm Hg and warm, N=3202			sBP <90 mm Hg or cold, N=793		
	No inotrope use, n=2890	Inotrope use, n=312	P value	No inotrope use, n=517	Inotrope use, n=276	P value
Daily life activities			0.67			0.36
Ambulatory*	2252 (78)	235 (77)		406 (79)	210 (76)	
Use of wheelchair (outdoor only)	218 (8)	29 (9)		33 (6)	19 (7)	
Use of wheelchair (outdoor and indoor)	277 (10)	28 (9)		54 (11)	25 (9)	
Bedridden	118 (4)	14 (5)		20 (4)	18 (7)	
Vital signs at presentation						
Systolic BP, mm Hg*†	152±33	134±27	<0.001	142±43	121±35	<0.001
Systolic BP <90 mm Hg	0 (0)	0 (0)	N/A	69 (13)	52 (19)	0.04
Diastolic BP, mm Hg	86±23	79±20	<0.001	85±27	74±24	<0.001
Heart rate, bpm	95±27	94±24	0.83	102±29	93±28	<0.001
Heart rate <60 bpm*	191 (7)	18 (6)	0.57	24 (5)	27 (10)	0.005
Rhythms at presentation						
Sinus rhythm	1569 (54)	201 (64)	<0.001	293 (57)	172 (62)	0.12
Atrial fibrillation/flutter	1121 (39)	81 (26)	<0.001	175 (34)	65 (24)	0.003
Tests at admission						
LVEF, %	49±16	38±16	<0.001	43±16	35±15	<0.001
HFrEF (EF <40%)*†	888 (31)	193 (62)	<0.001	249 (48)	195 (71)	<0.001
BNP, pg/mL‡	653 (365–1138)	1039 (577–1864)	<0.001	788 (465–1413)	1089 (498–1940)	<0.001
NT-pro-BNP, pg/mL‡	5417 (2577–11500)	9049 (3780–15852)	0.03	6601 (3151–17048)	9240 (4390–22347)	0.08
Serum creatinine, mg/dL	1.1 (0.8–1.6)	1.3 (0.9–1.8)	0.046	1.2 (0.9–1.7)	1.3 (1.0–2)	0.23
eGFR, mL/min/1.73 m^2	45.1 (29.4–61.3)	38 (26.3–54.8)	<0.001	42.7 (26.8–59.3)	35.5 (24.4–53)	0.01
eGFR <30 mL/min/1.73 m^2*†	748 (26)	99 (32)	0.03	150 (29)	106 (38)	0.007
Blood urea nitrogen, mg/dL	23 (17–34)	29 (20–45)	<0.001	26 (19–37)	30 (21–46)	<0.001
Albumin, g/dL	3.5±0.5	3.4±0.5	0.01	3.5±0.5	3.4±0.5	0.3
Albumin <3.0 g/dL*	389 (13)	37 (12)	0.43	79 (15)	50 (18)	0.3
Sodium, mEq/L	139±4.2	138±4.3	<0.001	139±4.3	137±5.4	<0.001
Sodium <135 mEq/L*	311 (11)	42 (13)	0.15	86 (17)	73 (26)	0.001
Potassium, mEq/dL	4.2±0.6	4.4±0.8	<0.001	4.3±0.7	4.5±0.8	0.002
Haemoglobin, g/L	114±23	117±24	0.019	119±24	121±24	0.68
Anaemia*†	1987 (69)	201 (64)	0.12	309 (60)	161 (58)	0.7

Continued

Table 1 Continued

	sBP ≥90 mm Hg and warm, N=3202			sBP <90 mm Hg or cold, N=793		
	No inotrope use, n=2890	Inotrope use, n=312	P value	No inotrope use, n=517	Inotrope use, n=276	P value
HF-related signs and symptoms at presentation						
NYHA Class III or IV	2485 (86)	267 (86)	0.96	476 (92)	262 (95)	0.15
Cold (peripheral hypoperfusion)	0 (0)	0 (0)	N/A	482 (93)	266 (96)	0.07
Paroxysmal nocturnal dyspnoea	1957/2787 (70)	227/299 (76)	0.039	360/488 (74)	181/251 (72)	0.63
Orthopnoea	2222/2819 (79)	243/299 (81)	0.32	421/491 (86)	222/257 (86)	0.81
Dyspnoea on exertion	2664/2793 (95)	280/299 (94)	0.18	458/486 (94)	232/251 (92)	0.34
Rale	2201/2822 (78)	246/302 (81)	0.17	404/490 (82)	205/258 (79)	0.32
Oedema	2253/2832 (80)	230/304 (76)	0.11	325/492 (66)	174/258 (67)	0.7
Elevated jugular venous pressure	2142/2738 (78)	239/295 (81)	0.27	375/486 (77)	193/251 (77)	0.93
Pleural effusion (moderate/severe)	2507/2870 (87)	272/311 (87)	0.96	412/511 (81)	218/274 (80)	0.72
Lung congestion (moderate/severe)	2655/2866 (93)	291/311 (94)	0.55	485/510 (95)	249/272 (92)	0.049
Medications at presentation						
Loop diuretic	1375 (48)	169 (54)	0.03	251 (49)	151 (55)	0.1
ACEI/ARB	1334 (46)	122 (39)	0.017	236 (46)	133 (48)	0.49
β-blocker	1087 (38)	125 (40)	0.4	207 (40)	122 (44)	0.26
MRA	463 (16)	73 (23)	<0.001	102 (20)	83 (30)	0.001
Thiazide	169 (6)	28 (9)	0.03	38 (7)	25 (9)	0.4
Tolvaptan	85 (3)	21 (7)	<0.001	21 (4)	39 (14)	<0.001
Digoxin	191 (7)	19 (6)	0.72	33 (6)	18 (7)	0.94
Warfarin	624 (22)	66 (21)	0.86	103 (20)	70 (25)	0.08
DOAC	310 (11)	21 (7)	0.03	49 (9)	23 (8)	0.59
Intravenous therapy within 24 hours of presentation						
Loop diuretic	2512 (87)	250 (80)	<0.001	413 (80)	183 (66)	<0.001
Vasodilators	1603 (55)	138 (44)	<0.001	319 (62)	102 (37)	<0.001
Carperitide	1074 (37)	93 (30)	0.01	228 (44)	75 (27)	<0.001
Nitrates	833 (29)	56 (18)	<0.001	167 (32)	41 (15)	<0.001
Vasopressor (norepinephrine)	39 (1)	17 (5)	<0.001	27 (5)	54 (20)	<0.001
Inotropes	0 (0)	312 (100)	N/A	0 (0)	276 (100)	N/A
Dopamine	0	48 (15)	N/A	0	38 (14)	N/A
Dobutamine	0	263 (84)	N/A	0	236 (86)	N/A

Continued

Table 1 Continued

	sBP ≥90 mm Hg and warm, N=3202			sBP <90 mm Hg or cold, N=793		
	No inotrope use, n=2890	Inotrope use, n=312	P value	No inotrope use, n=517	Inotrope use, n=276	P value
Phosphodiesterase inhibitor	0	14 (4)	N/A	0	23 (8)	N/A
Medications at discharge§						
Loop diuretic	2274 (82)	227 (81)	0.75	358 (76)	162 (76)	0.97
ACEI/ARB	1600 (58)	156 (56)	0.55	275 (59)	118 (55)	0.45
β-blocker	1778 (64)	196 (70)	0.04	336 (71)	157 (74)	0.55
MRA	144 (52)	1231 (44)	0.02	200 (43)	107 (50)	0.06

*Twenty-one risk-adjusting variables were selected for Cox proportional hazard models to estimate the risk for the postadmission and postdischarge outcomes.
†Eleven risk-adjusting variables included in the parsimonious models to estimate the risk for the all-cause death during index hospitalisation.
‡BNP and NT-pro-BNP were measured in 3535 and 685 patients, respectively.
§Percentages of these variables were expressed as proportions relative to number of patients at discharge.
ACEI, ACE inhibitor; ACS, acute coronary syndrome; ARB, angiotensin-receptor blocker; BMI, body mass index; BNP, brain-type natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass graft; DOAC, direct oral anticoagulant; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-pro-BNP, N-terminal-pro-BNP; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; sBP, systolic blood pressure; VF, ventricular fibrillation; VT, ventricular tachycardia.

748 (19%) had a cold profile and 76 (2%) had both a sBP <90 mm Hg and a cold profile on presentation. Accordingly, 793 patients (20%) were categorised into sBP <90 mm Hg or cold group, whereas the remaining 3202 patients (80%) were categorised into sBP ≥90 mm Hg and warm group. Overall, inotropes were used within 24 hours of hospital presentation in 588 (15%) patients. Among those, 276 (47%) were in the sBP <90 mm Hg/cold profile, whereas 312 (53%) were in the sBP ≥90 mm Hg/warm group (figure 1). In both groups, the patients with inotrope use were more likely to have ischaemic heart disease and cardiomyopathy as a HF aetiology, have a history of ventricular tachycardia/fibrillation, a lower left ventricular ejection fraction, a higher brain natriuretic peptide level, and a lower estimated glomerular filtration rate compared with the patients without inotrope use (table 1). Regarding the vital signs at presentation, the patients with inotrope use had lower sBP and were less likely to have atrial fibrillation/flutter as an initial rhythm at hospital presentation in both the sBP <90 mm Hg/cold group and sBP ≥90 mm Hg/warm group. Most of the study patients presented congestion-related signs and symptoms such as orthopnoea, dyspnoea on exertion, rales and elevated jugular venous pressure. The proportion of patients with congestion-related signs and symptoms was almost similar to the patients with inotrope use and no inotrope use in both groups (table 1). With respect to the medications at presentation, the proportion of patients receiving β-blockers was not significantly different between the patients with and without inotrope use, whereas the proportion of patients receiving mineralocorticoid receptor antagonists were significantly higher in the patients with inotrope use compared with no inotrope use in both the sBP <90 mm Hg/hypoperfusion group and the sBP ≥90 mm Hg/warm group (table 1). Regarding the intravenous vasoactive agents used within 24 hours of presentation, more than half of the patients with no inotrope use and nearly 40% of the patients with inotrope use received intravenous vasodilators within 24 hours of presentation in both groups. Vasopressor (ie, norepinephrine) was more frequently used in the sBP <90 mm Hg/hypoperfusion group than in the sBP ≥90 mm Hg/warm group. In both groups, it was more frequently used in the patients with inotrope use compared with no inotrope use. Overall, dobutamine was the most frequently used inotrope followed by dopamine and phosphodiesterase inhibitors (table 1). Patient characteristics across the three inotropic agents according to sBP and perfusion profile were shown in online supplemental table 1.

Long-term prognosis after admission

The median follow-up was 463 days with a 94% follow-up rate at 1 year.

During the follow-up period, 823 patients (26%) in the sBP ≥90 mm Hg/warm group and 282 patients (36%) in the sBP <90 mm Hg/cold group died. In both groups, the cumulative 1-year incidence of all-cause death in the

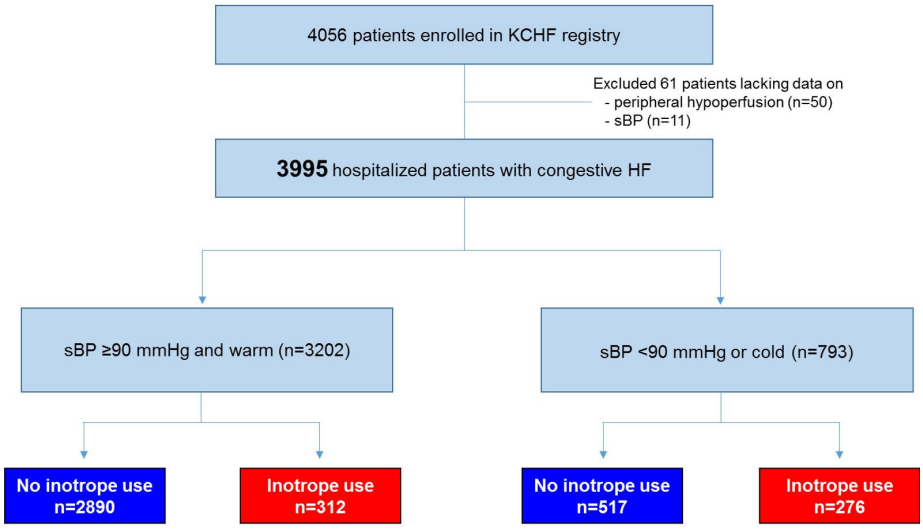

Figure 1 Study flow chart. HF, heart failure; KCHF, Kyoto Congestive Heart Failure; sBP, systolic blood pressure.

patients with inotrope use was significantly higher than in the patients without inotrope use (figure 2A,B). After adjustments for confounders, however, the risk of inotrope use relative to no inotrope use was significant only in the sBP ≥90 mm Hg/warm group, whereas adjusted excess risk of inotrope use relative to no inotrope use was not significant in the sBP <90 mm Hg/cold group (table 2). Likewise, despite a significantly higher cumulative 1 year incidence of cardiovascular death in the patients with inotrope use relative to no inotrope use in both groups (online supplemental figure 1A,B), the adjusted excess risk of inotrope use relative to no inotrope use for cardiovascular death from admission was only significant in the sBP ≥90 mm Hg/warm group but not in the sBP <90 mm Hg/cold group (table 2). Even when use of norepinephrine was added to inotropes use as the inotrope/vasopressor use, adjusted excess risk of inotrope/vasopressor use relative to no inotrope/vasopressor use for the primary outcome measure was significant in the sBP ≥90 mm Hg/warm group (adjusted HR, 1.43, 95% CI 1.16 to 1.77, p<0.001), but not in the sBP <90 mm Hg/cold group (adjusted HR, 1.30, 95% CI 0.98 to 1.72, p=0.07).

In-hospital prognosis

During index hospitalisation, 154 patients (5%) in the sBP ≥90 mm Hg/warm group and 110 patients (14%) in the sBP <90 mm Hg/cold group died. In both groups, the incidence of all-cause death during index hospitalisation was significantly higher in the patients with inotrope use than that in those with no inotrope use (figure 3A,B). The adjusted excess risk of inotrope use relative to no inotrope use for all-cause death during index hospitalisation was significant in both groups (table 2).

Postdischarge prognosis

A total of 3048 patients in the sBP ≥90 mm Hg/warm group and 683 patients in the sBP <90 mm Hg/cold group were discharged alive. In the sBP ≥90 mm Hg/warm group, 669 patients (21%) died and 759 patients (24%) were hospitalised for HF during the follow-up period, whereas

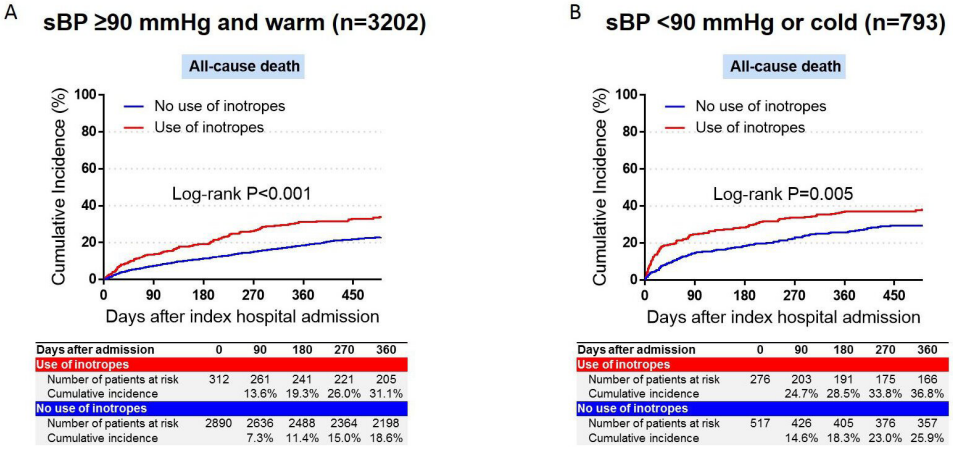

Figure 2 Kaplan–Meier curves for all-cause death across inotrope use according to sBP and perfusion profile. (A) patients with sBP ≥90 mm Hg and warm; (B) patients with sBP <90 mm Hg or cold. sBP, systolic blood pressure.

Table 2 Clinical outcomes across the patients with inotrope use and no inotrope use according to sBP and perfusion profile

Clinical outcomes	In-hospital or cumulative 1-year incidence (%)		Inotrope use versus no inotrope use			
	Inotrope use	No inotrope use	Unadjusted HR (95% CI)	P value	Adjusted HR* (95% CI)	P value
sBP ≥90 mm Hg and warm, n=3202						
Primary outcome measure						
All-cause death after admission	94 (31.1)	524 (18.6)	1.54 (1.25 to 1.87)	<0.001	1.36 (1.09 to 1.72)	0.006
Secondary outcome measures						
Cardiovascular death after admission	70 (24.2)	310 (11.3)	1.87 (1.46 to 2.37)	<0.001	1.49 (1.13 to 1.94)	0.004
In-hospital all-cause death	33 (10.6)	121 (4.1)	2.71 (1.78 to 4.01)	<0.001	1.98 (1.28 to 3.07)	0.002
Post-discharge all-cause death	61 (22.9)	421 (15.7)	1.32 (1.03 to 1.67)	0.03	1.25 (0.96 to 1.62)	0.10
HF hospitalisation	76 (30.3)	577 (22.7)	1.35 (1.07 to 1.68)	0.01	1.26 (0.99 to 1.61)	0.07
sBP <90 mm Hg or cold, n=793						
Primary outcome measure						
All-cause death after admission	101 (36.8)	130 (25.9)	1.42 (1.12 to 1.80)	0.004	1.28 (0.96 to 1.69)	0.09
Secondary outcome measures						
Cardiovascular death after admission	75 (28.9)	91 (18.7)	1.49 (1.13 to 1.97)	0.006	1.35 (0.96 to 1.88)	0.08
In-hospital all-cause death	63 (22.8)	47 (9.1)	2.96 (1.97 to 4.48)	<0.001	2.27 (1.45 to 3.57)	<0.001
Postdischarge all-cause death	39 (19.7)	88 (19.0)	0.93 (0.67 to 1.28)	0.68	0.88 (0.60 to 1.30)	0.52
HF hospitalisation	54 (27.7)	108 (25.5)	1.15 (0.84 to 1.54)	0.38	1.10 (0.76 to 1.58)	0.62

*Adjusted for the clinically relevant variables listed in table 1.
HF, heart failure; sBP, systolic blood pressure.

172 patients (22%) died and 186 patients (24%) were hospitalised for HF in the sBP <90 mm Hg/cold group. In the sBP ≥90 mm Hg/warm group, cumulative 1-year incidences of all-cause death after discharge and HF hospitalisation were significantly higher in the patients with inotrope use (figure 3C,E), whereas there was negligible difference between the patients with inotrope use and no inotrope use in the sBP <90 mm Hg/cold group (figure 3D,F). After adjustment by confounders, excess risks of inotrope use relative to no inotrope use for all-cause death after discharge and HF hospitalisation were not significant in both groups (table 2).

DISCUSSION

This study from a large contemporary Japanese cohort demonstrated that 15% of the patients hospitalised with congestive HF received inotropes within 24 hours of hospital presentation. Fifty-three per cent of those patients did not have the guideline-recommended clinical indications of inotrope use such as sBP <90 mm Hg and a cold profile. Long-term mortality risk of initial inotrope use relative to no inotrope use was significant in the sBP ≥90 mm Hg/warm group, but not in the sBP <90 mm Hg/cold group. There were no differences in the risk for post-discharge all-cause death and HF hospitalisation between the inotrope use and no inotrope use in both sBP ≥90 mm Hg/warm group and sBP <90 mm Hg/cold group.

In addition to diuretics and vasodilators, inotropes have long been used for the treatment of decompensated HF, particularly for patients with cardiogenic shock or signs of impaired perfusion. However, previous studies demonstrated that the use of inotropes in the treatment of acute decompensated HF was associated with short-term adverse outcomes.[6–8 18] Thus, US and European guidelines restrict the use of inotropic agents unless the patients have symptomatic hypotension or signs of peripheral hypoperfusion.[1 2] Despite negative implications from the previous observational studies and guideline restrictions, our study demonstrated that inotrope use is still common in the current real world of hospitalised HF patients with 15% of the study participants receiving inotropes within 24 hours of hospital presentation. Notably, more than half of the patients initially treated with inotropes did not exhibit hypotension or signs of peripheral hypoperfusion on hospital presentation. The results were similar to those from the European Society of Cardiology Heart Failure Long-Term registry in which 12% of the study patients received inotropes and/or vasopressors during the first 24 hours after admission and 45.7% of these patients exhibited signs of peripheral hypoperfusion.[10] In our study, crude 1-year mortality risk of the patients initially treated with inotropes was 31.1% in the sBP ≥90 mm Hg/warm group

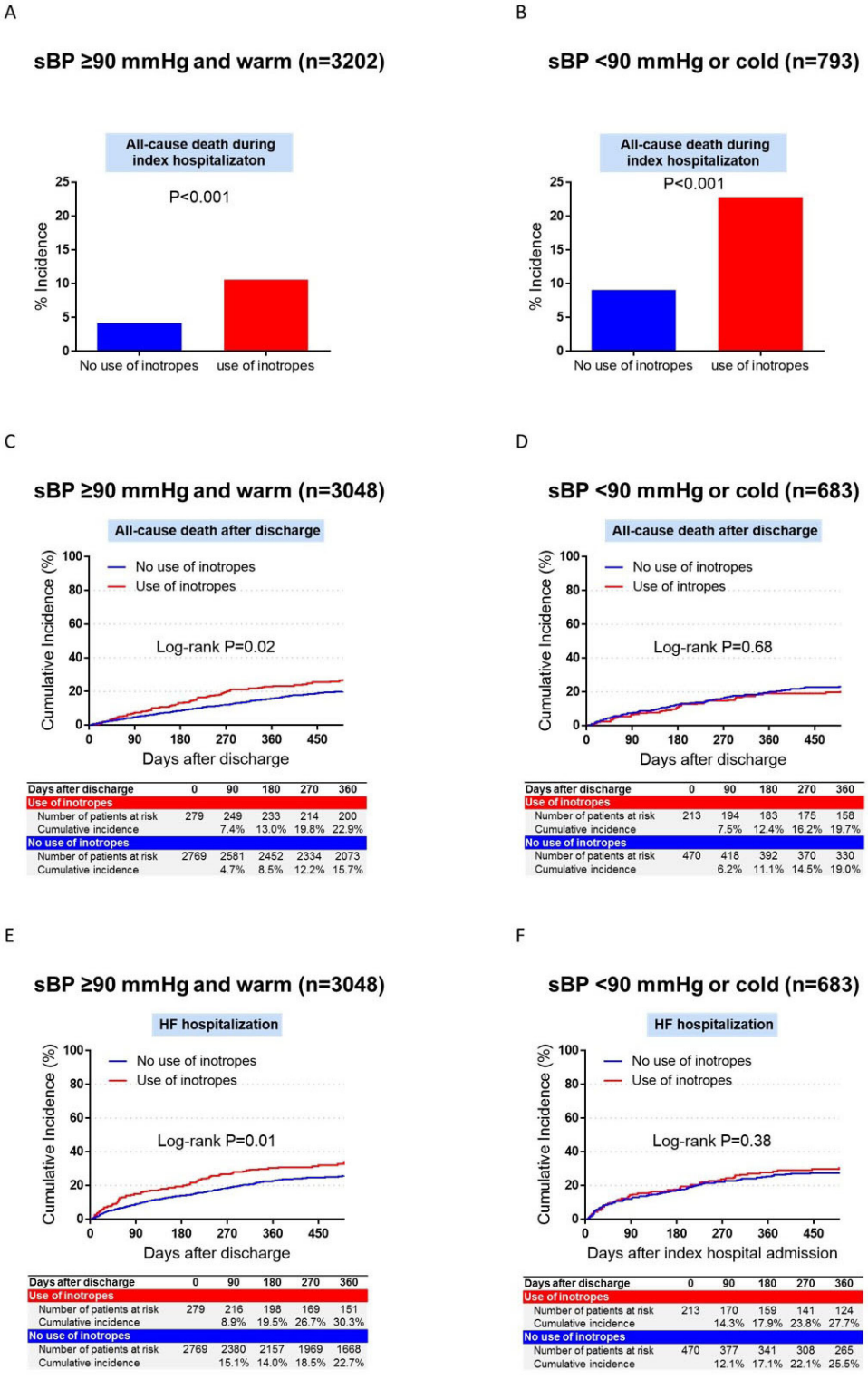

Figure 3 Incidence of all-cause death during index hospitalisation (A, B), all-cause death after discharge (C, D) and HF hospitalisation (E, F). A, C and E, patients with sBP ≥90 mm Hg and warm; B, D and F, patients with sBP <90 mm Hg or cold. HF, heart failure; sBP, systolic blood pressure.

and 36.8% in the sBP <90 mm Hg/cold group, both of which were much higher than that of the patients without inotrope use. However, inotrope use had a different effect size for long-term mortality across the two groups. Adjusted excess risk of inotrope use relative to no inotrope use for 1-year mortality was significant among the patients without hypotension or signs of impaired perfusion, whereas it was neutral among the patients presenting with hypotension or a cold profile. The results were similar with the previous reports by Kang *et al* showing that inotrope use was an independent predictor for in-hospital and 1-month postdischarge mortality in patients with initial sBP ≥90 mm Hg, but not in patients with an initial

sBP <90 mm Hg.[19] However, the categorisation of our patients into the sBP <90 mm Hg or cold group was mainly driven by 'cold' profile rather than sBP <90 mm Hg as more than 90% of this group had cold profile, whereas 85% had sBP ≥90 mm Hg. Given the limited options for medical management of decreased cardiac output and impaired peripheral organ perfusion, inotrope use might still be an option for patients with a cold profile. On the other hand, our results might support inappropriateness of inotrope use for haemodynamically stable patients with adequate peripheral perfusion, enforcing the current guidelines that discourage the routine use of inotropes. However, it should be noted that the present results should be interpreted carefully. Although the present results come from a large contemporary HF cohort, they provide only a snapshot of current real-world clinical practice. Its observational design per se precludes the demonstration of a causal relationship between initial inotropic treatment and outcomes. We cannot deny the possibility that the increased mortality associated with the use of inotropes may be attributed to patient characteristics rather than drug-specific characteristics.

A previous trial comparing the outcomes of dobutamine with nesiritide among patients with acute decompensated HF showed that even short-term infusion of dobutamine within 3 days resulted in a significantly higher 6 month mortality compared with nesiritide.[20] Similarly, a 24-hour infusion of dobutamine was associated with a significantly higher 6-month mortality compared with levosimendan. These results suggest that even short-term exposure to catecholamines could affect long-term prognosis.[21] Irreversible catecholamine-induced damage to cardiac myocytes has been suggested as an underlying mechanism.[21] However, we found that a high 1-year mortality risk in the inotrope stratum was mainly driven by a higher in-hospital mortality, whereas the risks of postdischarge mortality and HF hospitalisation were comparable between inotrope stratum and no inotrope stratum in both the sBP ≥90 mm Hg/cold and sBP <90 mm Hg/warm groups. These results were in line with a recent observational study reporting a lack of association between inotrope use and 6 month post-discharge mortality in patients with reduced EF.[22] The results may suggest that adverse effects potentially induced by inotropes such as direct myocardial toxicity, increased oxygen consumption and arrhythmogenesis are temporal and do not last a long time. The results highlight unmet needs for the development of a more effective and safe treatment strategy targeting the initial phase of HF to overcome the imminent critical condition seen in our patients in the inotrope stratum.

Limitations

This study had several limitations. First, because of its observational nature, the decision to use vasoactive agents was made by the attending physicians, which is inherently subject to selection bias and confounding. Second, although detailed data in our dataset enabled intensive adjustment with most conceivable and previously established confounders, we were unable to exclude the influence of other unmeasured confounding factors. In addition, for the evaluation of all-cause death during index hospitalisation, we used parsimonious models because of a small number of patients with outcome. Third, the exact dose of agents and the duration of their use were not available in our dataset. Thus, we were unable to distinguish low- and high-dose infusions of inotropes. Finally, although this study included nearly 4000 patients, the sample size was still insufficient to separately analyse the impact of individual drugs categorised as inotropes.

In conclusion, this study demonstrated the current use of inotropes in initial in-hospital treatment of HF in real-world practice. Inotropes are still commonly used against guideline recommendations. Inotrope treatment is associated with a high long-term mortality risk, particularly when used in the absence of shock or peripheral hypoperfusion. Development of standardised and evidence-based approaches to initial HF treatment might improve clinical outcomes.

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Supplemental Material

Supplemental Table 1 Patient characteristics across the 3 inotropes according to sBP and perfusion profile

	Inotrope use in the patients with sBP ≥90mmHg and warm (n=312)			Inotrope use in the patients with sBP <90mmHg or cold (n=276)		
	Dobutamine* n=263 (84%)	Dopamine n=38 (12%)	Phosphodiesterase inhibitors n=11 (4%)	Dobutamine † n=236 (86%)	Dopamine n=24 (9%)	Phosphodiesterase inhibitors n=16 (6%)
Clinical characteristics						
Age, years	81 (68–87)	81 (74–87)	82 (75–88)	79 (67–85)	78 (72–83)	74 (70–79)
Female	103 (39)	22 (58)	3 (27)	79 (33)	5 (21)	7 (44)
BMI, kg/m^2	22.3 ± 4.5	21.6 ± 3.3	21.7 ± 3.0	22.0 ± 4.4	21.7 ± 3.5	22.6 ± 4.5
Etiology						
Ischemic	87 (33)	8 (21)	4 (36)	75 (32)	9 (38)	4 (25)
ACS	18 (7)	3 (8)	2 (18)	32 (14)	4 (17)	1 (6)
Cardiomyopathy	62 (24)	10 (26)	0 (0)	71 (30)	4 (17)	7 (44)
Valuvular	53 (20)	7 (18)	4 (36)	27 (11)	5 (21)	3 (19)
Medical history						

Prior hospitalization for HF	108 (41)	15 (39)	4 (36)	109 (46)	13 (54)	4 (25)
Atrial fibrillation or flutter	77 (29)	18 (47)	3 (27)	74 (31)	10 (42)	1 (6)
Hypertension	161 (61)	22 (58)	9 (82)	129 (55)	11 (46)	7 (44)
Diabetes mellitus	95 (36)	18 (47)	4 (36)	101 (43)	12 (50)	8 (50)
Dyslipidemia	88 (33)	19 (50)	6 (55)	89 (38)	9 (38)	6 (38)
Prior myocardial infarction	79 (30)	8 (21)	2 (18)	60 (25)	6 (25)	5 (31)
Prior stroke	40 (15)	11 (29)	2 (18)	37 (16)	4 (17)	2 (13)
Current smoking	27 (10)	5 (13)	0 (0)	27 (11)	1 (4)	3 (19)
Ventricular tachycardia/fibrillation	21 (8)	2 (5)	0 (0)	27 (11)	3 (13)	1 (6)
Chronic lung disease	32 (12)	5 (13)	3 (27)	29 (12)	2 (8)	2 (13)
Vital signs at presentation						
sBP, mmHg	132 ± 27	141 ± 34	143 ± 16	121 ± 35	107 ± 33	138 ± 31
sBP <90mmHg	0 (0)	0 (0)	0 (0)	46 (19)	6 (25)	0 (0)

Heart rate, bpm	96 ± 24	82 ± 29	85 ± 17	93 ± 27	83 ± 29	109 ± 37
Heart rate <60 bpm	9 (3)	9 (24)	0 (0)	22 (9)	5 (21)	0 (0)
Rhythms at presentation						
Sinus rhythm	172 (65)	21 (55)	8 (73)	147 (62)	13 (54)	12 (75)
Atrial fibrillation/flutter	66 (25)	13 (34)	2 (18)	54 (23)	8 (33)	3 (19)
Tests at admission						
LVEF, %	36 ± 15	45 ± 16	48 ± 15	34 ± 14	36 ± 21	34 ± 16
HFrEF (EF<40%)	175 (67)	14 (37)	4 (36)	167 (72)	15 (65)	13 (81)
BNP, pg/mL ‡	1049 (583–1920)	831 (485–1450)	1406 (934–2561)	1072 (493–1891)	1231 (538–2006)	1275 (721–2000)
NT–proBNP, pg/m ‡	8718 (4531–14615)	19538 (2420–47100)	N/A	9330 (5342–23018)	2346 (2326–13308)	N/A
Serum creatinine, mg/dL	1.24 (0.93–1.75)	1.3 (0.96–2.1)	1.8 (1.3–3.0)	1.34 (0.95–1.95)	2.01 (1.15–3.37)	1.09 (0.90–1.33)
eGFR, mL/min/1.73m^2	40.1 (26.9–56)	34.3 (21.8–47.7)	29.4 (16.0–38.0)	35.5 (24.9–53.6)	23.5 (14.0–46.0)	42.9 (32.6–64.3)
eGFR <30mL/min/1.73m^2	124 (47)	19 (50)	8 (73)	89 (38)	14 (58)	3 (19)

Blood urea nitrogen, mg/dL	28 (19–45)	29 (19–50)	33 (27–57)	30 (21–46)	35 (24–60)	25 (17–33)
Albumin, g/dL	3.4 ± 0.5	3.3 ± 0.5	3.4 ± 0.5	3.4 ± 0.04	3.3 ± 0.1	3.5 ± 0.1
Sodium, mEq/L	139 ± 4.1	138 ± 5.5	138 ± 2.6	137 ± 5.6	137 ± 4.4	137 ± 3.7
Potassium, mEq/dL	4.4 ± 0.8	4.4 ± 0.8	4.8 ± 0.8	4.5 ± 0.8	4.7 ± 1.0	4.4 ± 0.7
Hemoglobin, g/dL	11.9 ± 2.4	10.6 ± 2.0	10.3 ± 2.1	12.3 ± 2.4	10.5 ± 2.2	11.5 ± 2.6
Anemia	160 (61)	32 (84)	9 (82)	131 (56)	20 (83)	10 (63)
Medications at presentation						
Loop diuretic	142 (54)	22 (58)	5 (45)	132 (56)	14 (58)	5 (31)
ACEI/ARB	102 (39)	16 (42)	4 (36)	115 (49)	13 (54)	5 (31)
β–blocker	104 (40)	18 (47)	3 (27)	107 (45)	12 (50)	3 (19)
MRA	65 (25)	8 (21)	0 (0)	73 (31)	7 (29)	3 (19)
Thiazide	24 (9)	4 (11)	0 (0)	22 (9)	1 (4)	2 (13)
Tolvaptan	16 (6)	4 (11)	1 (9)	29 (12)	8 (33)	2 (13)
Digoxin	17 (6)	1 (3)	1 (9)	15 (6)	2 (8)	1 (6)

Warfarin	52 (20)	13 (34)	1 (9)	58 (25)	10 (42)	2 (13)
DOAC	18 (7)	3 (8)	0 (0)	20 (8)	1 (4)	2 (13)
Intravenous therapy within 24 hours of presentation						
Loop diuretic	214 (82)	183 (66)	10 (91)	155 (66)	17 (71)	11 (69)
Carperitide	83 (32)	7 (18)	3 (27)	66 (28)	2 (8)	7 (44)
Nitrates	45 (17)	9 (24)	2 (18)	37 (16)	2 (8)	2 (13)
Noradrenaline	13 (5)	2 (5)	2 (18)	50 (21)	3 (13)	1 (6)

*10 patients (4%) and 3 patients (1%) also received dopamine and phosphodiesterase inhibitors within 24 h of presentation, respectively.

† 14 patients (6%) and 7 patients (3%) also received dopamine and phosphodiesterase inhibitors within 24 h of presentation, respectively.

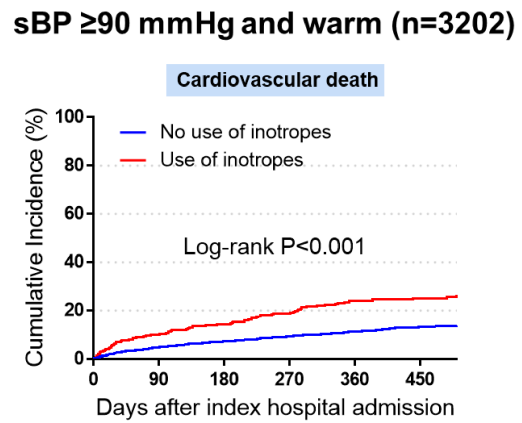
‡ BNP and NT–proBNP were measured in 544 and 67 patients, respectively

ACEI, angiotensin–converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin–receptor blocker; BMI, body mass index; BNP, brain–type natriuretic peptide; DOAC, direct oral anticoagulant; EF, ejection fraction; eGFR, estimated glomerular filtration

rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT–proBNP, N–terminal–proBNP; sBP, systolic blood pressure

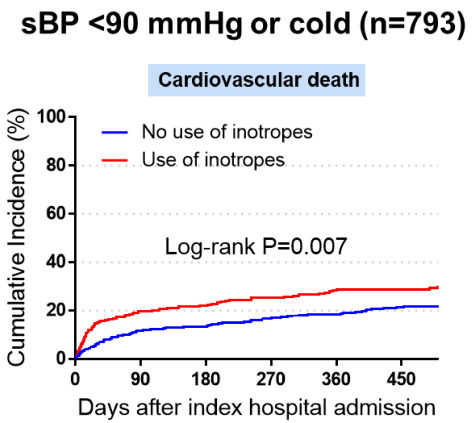
Supplemental Figure 1

A



Days after admission	0	90	180	270	360
Use of inotropes					
Number of patients at risk	312	261	241	221	205
Cumulative incidence		10.1%	14.3%	18.7%	24.2%
No use of inotropes					
Number of patients at risk	2890	2636	2488	2364	2198
Cumulative incidence		4.8%	7.3%	9.4%	11.3%

B



Days after admission	0	90	180	270	360
Use of inotropes					
Number of patients at risk	276	203	191	178	166
Cumulative incidence		19.6%	22.0%	25.4%	28.%
No use of inotropes					
Number of patients at risk	517	426	410	376	361
Cumulative incidence		11.8%	13.5%	16.9%	18.5%