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ORIGINAL ARTICLE
Heart failure

Beta-blocker initiation under dobutamine infusion in acute advanced heart failure: a target trial emulation with observational data

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Aims

In patients with advanced heart failure requiring dobutamine infusion, it is usually recommended to initiate beta-blockers after weaning from dobutamine. However, beta-blockers are sometimes initiated under dobutamine infusion in a real-world scenario. The association between such early beta-blocker initiation with clinical outcomes is unknown. Therefore, this study investigates the association between initiating beta-blockers under dobutamine infusion and survival outcomes.

Methods and results

This observational study with a multicentre inpatient-care database emulated a pragmatic randomized controlled trial (RCT) of the beta-blocker initiation strategy. First, 1151 patients on dobutamine and not on beta-blockers on the day of heart failure admission (Day 0) were identified. Among 1095 who met eligibility criteria, patients who were eventually initiated beta-blockers under dobutamine infusion by Day 7 (early initiation strategy) were 1:1 matched to those who were not initiated (conservative strategy). The methods of cloning, censoring, and weighting were applied to emulate the target trial. Patients were followed up for up to 30 days. The primary outcome was all-cause death. Among 780 matched patients (median age, 81 years), the adjusted hazard ratio was 1.11 (95% confidence interval 0.75–1.64, $P = 0.59$) for the early initiation strategy. The estimated 30-day all-cause mortalities in the early initiation strategy and the conservative strategy were 19.3% (10.6–30.7) and 16.2% (9.2–25.3), respectively. The results were consistent when we used different days to determine strategies (i.e. 5 and 9) instead of 7 days.

Conclusion

The present observational study emulating a pragmatic RCT found no positive or negative association between beta-blocker initiation under dobutamine infusion and overall survival.

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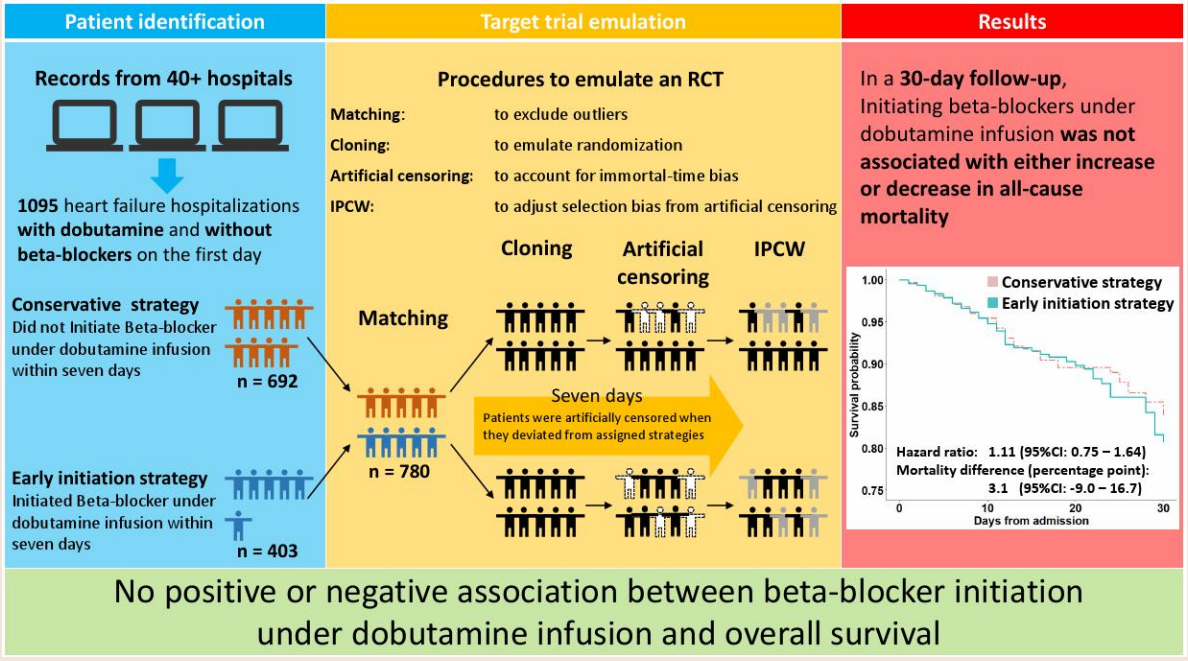
Graphical Abstract



In a panel of patient identification, 'strategy' indicates the eventual clinical courses that patients actually followed. In the target trial emulation, all matched patients were cloned into two replicates and assigned to both treatment strategies. Then, they were artificially censored when they deviated from assigned strategies. CI, confidence interval; HR, hazard ratio; IPCW, inverse probability of censoring weighting; RCT, randomized controlled trial.

Keywords Beta-blockers • Dobutamine • Target trial emulation • Advanced heart failure

Introduction

Beta-blockers are the cornerstone of heart failure treatment to improve long-term outcomes, and their prompt initiation and up-titration are recommended by guidelines.[1–4] The American Heart Association/the American College of Cardiology guideline for heart failure management suggests that the appropriate timing of beta-blocker initiation is when patients no longer require inotropes.[2] However, several real-world studies[5–7] and case reports[8–12] indicate that beta-blockers are sometimes initiated concurrently with dobutamine infusion.

The reasons behind the clinical practice of initiating beta-blockers under dobutamine infusion remain unclear. Currently, no evidence, guidelines, or physiological rationale seem to provide strong support for this practice. As mentioned in some case reports,[9,12] physicians may expect beta-blockers to provide antiarrhythmic or cardioprotective effects even under dobutamine infusion. Additionally, physicians may want to initiate beta-blockers early to secure their long-term use, as suggested in previous studies.[13,14] Given that such practice seems to be largely based on expert opinions, further investigations on its effectiveness are needed to guide physicians in treating patients with advanced heart failure.

Although the safety of sustained beta-blocker therapy has been demonstrated in heart failure hospitalizations without requiring inotropic agents,[13] no studies have investigated the safety of initiating beta-blockers under dobutamine infusion in patients with severe heart failure, presumably because of the lack of supportive rationales. Therefore, we conducted an observational study with a multicentre inpatient-care database using the framework of target trial emulation[15] that allows the use of observational data for causal questions wherein conducting a randomized controlled trial (RCT) is practically difficult or requires more evidence. The present study was designed to explicitly emulate an RCT of initiating beta-blockers under dobutamine infusion.

Methods

Study design

In this study, we aimed to emulate a pragmatic RCT to evaluate the effect of beta-blocker initiation under dobutamine infusion on all-cause mortality within 30 days. In this hypothetical pragmatic RCT, patients assigned to an intervention arm were initiated beta-blockers under dobutamine infusion within 7 days from admission. Conversely, patients assigned to a control arm were not initiated beta-blockers under dobutamine infusion within 7 days from admission. The study was reported following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines[16] (see Supplementary material online, *Table S1*). A detailed comparison of the target trial and the present study is given in Supplementary material online, *Table S2*.

Treatment strategies

(1) Early initiation strategy: The early initiation strategy was defined as initiating beta-blockers with continuing dobutamine during the grace period. The grace period was set to 7 days from the day of admission.
(2) Conservative strategy: The conservative strategy was defined as refraining from initiating beta-blockers during the grace period if the patient was under the use of dobutamine. After the grace period, there were no restrictions regarding beta-blocker initiation and dobutamine infusion.

Data sources

We obtained multicentre inpatient-care data from the Medical Data Vision database (http://www.mdv.co.jp), one of the largest commercial healthcare databases in Japan, consisting of laboratory and administrative data from more than 200 acute-care hospitals nationwide. The available data included the date of birth, sex, disease codes translatable into the International Classification of Diseases, 10th revision (ICD-10),[17] procedural and prescription records, discharge status, and laboratory data. The administrative data were standardized nationwide because they have been used in Japan's inpatient reimbursement system.[18] A previous study reported the high specificity and moderate sensitivity of these administrative data.[19] Laboratory values were available from a subset of participating hospitals, and the available dates varied across each hospital.

Study population

From the database, we identified 58 045 patients hospitalized from 10 October 2016 to 31 November 2021, with recorded reasons of congestive heart failure (ICD-10: I500, as previously validated in the Japanese administrative database[20]). Among them, the study cohort was retrospectively identified with the following inclusion and exclusion criteria. These criteria were designed to exclude those with too severe clinical status to consider initiating beta-blockers. The inclusion criteria were (i) the use of dobutamine on the day of admission (Day 0), (ii) no use of beta-blockers on Day 0, and (iii) available laboratory data on Day 0 or 1. Patients were excluded if (i) age ≤ 18; (ii) death within 24 h from admission; (iii) transferred to other facilities on Day 0; (iv) underwent surgery with general anaesthesia, percutaneous coronary intervention, or transcatheter aortic valve replacement on Day 0; or (v) used temporary cardiac pacing, percutaneous mechanical circulatory support device, percutaneous cardiopulmonary support, intra-aortic balloon pump, or adrenaline on Day 0. The definition of beta-blockers included both intravenous and oral agents available in Japan with a few exceptions: (i) intravenous esmolol, which is approved for use only during general anaesthesia; and (ii) a brand of intravenous landiolol (Corebeta, Ono Pharmaceutical Co., Osaka, Japan), which is approved only for heart rate control in coronary artery computed tomography. All beta-blockers considered in the study are listed in Supplementary material online, *Table S3*.

After the initial inclusion and exclusion process, we additionally excluded patients with extreme background characteristics using propensity-score matching with calliper. Patients who eventually followed the early initiation strategy were 1:1 matched to those who eventually did not. The propensity score was derived from a logistic regression model, and the matching was based on nearest-neighbour matching with a calliper of 0.10. Unmatched patients were excluded from the analysis. Missing data on covariates were imputed using a random forest algorithm.[21] All predictor variables were used for matching, and these variables and other potentially relevant variables were used for imputation (see the Predictor variables section).

Predictor variables

The following variables were used for matching, artificial censoring prediction, and weighting procedure: age, sex, blood pressure on admission (recorded in three categories in the database: <100, 100–140, or >140 mmHg), body mass index (BMI), haemoglobin, albumin, sodium, potassium, blood urea nitrogen, estimated glomerular filtration rate (eGFR), and N-terminal pro-brain natriuretic peptide (NT-pro-BNP). In addition, we incorporated potentially relevant variables with <30% missingness for imputing missing data (see Supplementary material online, *Tables S4* and *S5*). Laboratory data on Day 0 or 1 (only when there were no available laboratory data on Day 0) were used as predictor variables. When NT-proBNP was not measured, but brain natriuretic peptide was available, NT-proBNP was approximated with brain natriuretic peptide multiplied by 6.25.[22] We adopted the single ratio because our data had no information on atrial fibrillation at admission, which may affect the ratio.[22]

Outcomes

The primary outcome was all-cause mortality. To compare the outcome between strategies, we estimated a hazard ratio of all-cause death for the early initiation strategy compared with the conservative strategy with a weighted Cox proportional hazard model. Patients were followed up until an occurrence of the outcome, discharged from the hospital (i.e. lost to follow-up), or 30 days from their admission, whichever occurred first. Also, the 30-day absolute risk of the primary outcome and the restricted mean survival time (RMST)[23] for each strategy were estimated.

Statistical analysis

We employed methods of cloning, censoring, and weighting to deal with immortal time bias in line with previous investigations.[15,24–26] Immortal time bias refers to the bias from a period during which, by design, the outcome could not occur. In our study, patients who followed the early initiation strategy must have been alive until they were initiated beta-blockers, whereas those in the conservative strategy could have died soon after the follow-up began. Adjusting the baseline characteristics with matching and regression is irrelevant to the immortal time bias.[27] The detailed methodologies are elaborated in the Supplementary material online, *Methods*. We employed those methods as the following steps.

First, to emulate randomization, participants were cloned into two replicates, and each replicate was assigned to each strategy at the start of the follow-up (cloning step). Second, participants' survival, end of follow-up, and use of beta-blockers and dobutamine were assessed at daily intervals. Replicates were artificially censored when they deviated from the assigned strategy (the artificial censoring step). Third, to minimize the potential selection bias arising from artificial censoring, participants were weighted with a time-varying inverse probability of censoring weight (IPCW). The probability of being censored was calculated with a Cox proportional hazard model by adjusting predictor variables (see the Predictor variables section) for each strategy arm. Participants were also weighted with an inverse probability of treatment weight (IPTW) based on the propensity score calculated in the matching procedure (see the Study population section). Stabilized weight with a truncation of upper and lower outliers (2.5% each) was used for IPTW and IPCW to mitigate the influence of too extreme weights on results.[28] Finally, the hazard ratio and the 95% confidence intervals (95% CIs) for the early initiation strategy were derived from the Cox proportional hazard regression. Also, the mortality rate and the RMST for each strategy were calculated based on the weighted survival curve. The 95% CI of the mortality and the RMST were estimated by using a non-parametric bootstrap with 1000 samples. The bootstrap procedure was applied for the post-matched samples[29] with accounting for the matching pair. All bootstrapped samples repeated the statistical analysis from the cloning step. Differences were considered statistically significant at $P \leq 0.05$. All statistical analyses were performed using R4.1.2.

Sensitivity analysis

The following two sensitivity analyses were conducted to test the consistency of the main results. First, we repeated the main analysis by redefining the grace period of 5 and 9 days to account for the arbitrariness of setting the grace period as 7 days. Second, to estimate survival outcomes for a more extended period, we conducted the analysis of 60-day follow-up with the following additional assumption: patients who were discharged or transferred with outcome records of disease recovery were regarded as alive until Day 60 because the database utilized in the study could not follow up patients who were moved to other facilities or discharged.

Additional analysis

To assess whether the main analysis adequately adjusted selection bias and immortal time bias, we conducted two additional analyses. First, the primary outcomes were evaluated without adjusting selection bias (i.e. without IPTW and IPCW, but with cloning and artificial censoring). Second, we repeated the main analysis without accounting for immortal time bias (i.e. without cloning, censoring, and IPCW but with IPTW). We assumed that both analyses would erroneously favour the early initiation strategy because participants who eventually followed the strategy would have milder clinical status and should have been alive until they were initiated beta-blockers.

Ethical review of study

The Institutional Review Board of Kyoto University approved this study and waived the requirement of informed consent owing to the use of de-identified data (R3925; 15 May 2023; 'The Timing of Beta-Blocker

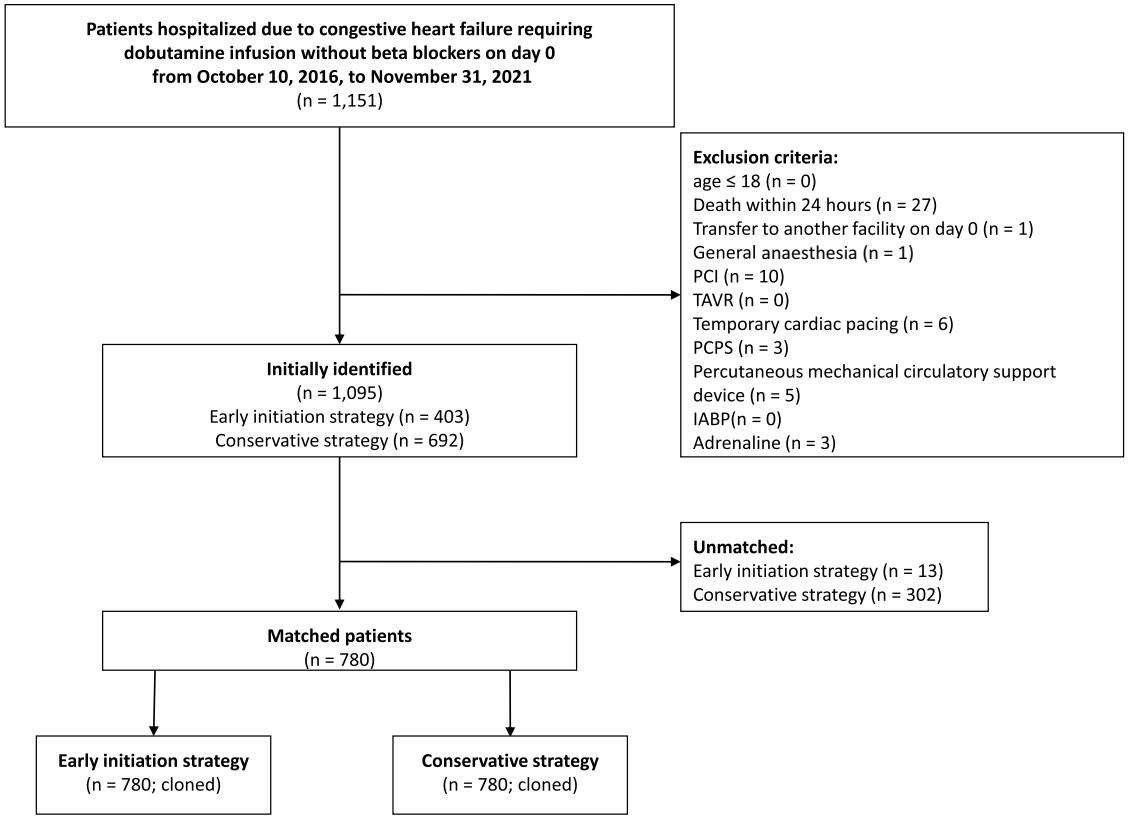


Figure 1 A flow of study sample selection. Early initiation strategy: initiating beta-blockers with continuing dobutamine within 7 days. Conservative strategy: refraining from initiating beta-blockers within 7 days if the patient was using dobutamine. IABP, intra-aortic balloon pump; PCI, percutaneous cardiac intervention; PCPS, percutaneous cardiopulmonary support; TAVR, transcatheter aortic valve replacement.

Initiation in Advanced Heart Failure'). All methods were conducted in accordance with the Declaration of Helsinki.

Results

From 1497 patients hospitalized due to congestive heart failure and initially treated with dobutamine, we identified 1151 patients who did not use beta-blockers on the day of admission. Of those, 1095 patients met the eligibility criteria (eventual clinical course; 403: early initiation strategy, 692: conservative strategy). After propensity-score matching, 780 patients (390: early initiation strategy, 390: conservative strategy) were finally enrolled (*Figure 1* and Supplementary material online, *Figure S1*). At baseline, the median age of the enrolled patients was 81.0 (interquartile range 70.0–87.0) years, and 38.5% ($n = 300$) were women. The median BMI, eGFR, and NT-proBNP were 22.0 (19.9–24.5) kg/m^2, 40.1 (24.3–55.7) mL/min/1.73 m^2, and 7965.0 (4597.2–11 767.0) pg/dL, respectively. On the day of admission, 66.8% ($n = 521$) were treated with intravenous diuretics, 31.7% ($n = 247$) received intravenous vasodilators, and 9.4% ($n = 73$) required an arterial line (*Table 1*).

During the 30-day follow-up, 74.4% ($n = 580$) initiated beta-blockers, 11.5% ($n = 90$) had died, and 60.6% ($n = 473$) were discharged alive. Among 90 patients who died during the follow-up, 52 were recorded as having died of heart failure and 38 of other causes. The median days of follow-up were 8.00 (4.00–12.00). More than 90% of the beta-blockers used within 7 days were bisoprolol or carvedilol (371/390). Among patients who had not been initiated beta-blockers under dobutamine infusion by Day 7, 48.7% (190/390) were eventually initiated beta-blockers, and the most used class was carvedilol (95/190), followed by bisoprolol (85/190) (see Supplementary material online, *Table S6*).

In the main analysis (i.e. after cloning, censoring, and weighting), the adjusted hazard ratio was 1.11 (0.75–1.64, $P = 0.59$) for the early initiation strategy (*Figure 2*). The estimated 30-day all-cause mortality was 19.3% (95% CI 10.6–30.7) in the early initiation strategy and 16.2% (9.2–25.3) in the conservative strategy [difference in percentage points: 3.1% (−9.0 to 16.7); $P = 0.66$]; and the RMST was 27.7 (26.3–28.6) days in the early initiation strategy and 27.8 (26.6–28.8) days in the conservative strategy [difference: −0.1 days (−1.2 to 1.6); $P = 0.92$]. In addition, there was no clear difference in the results across the beta-blockers used in the early initiation strategy arm [bisoprolol, hazard ratio: 1.13 (0.69–1.86); carvedilol, hazard ratio: 1.01 (0.57–1.77), Supplementary material online, *Figure S2*]; or the cause of death [death from heart failure, hazard ratio: 1.08 (0.65–1.79); death from other causes, hazard ratio: 1.16 (0.63–2.13); see Supplementary material online, *Figure S3*].

In sensitivity analyses, the early initiation strategy did not show better survival rates than the conservative strategy. The hazard ratios for the early initiation strategy in the analysis with 5 and 9 days of the grace period were 1.05 (0.70–1.59) and 1.02 (0.72–1.45), respectively (*Table 2* and Supplementary material online, *Figure S4*). In a 60-day follow-up estimation in which patients discharged or transferred with records of disease recovery were assumed to be alive until the end

Table 1 **Summary of patient characteristics by eventual clinical course, before and after propensity-score matching**

Characteristics	Pre-matching	Pre-matching	ASMD	Post-matching	Post-matching	ASMD
Eventual clinical course	Early initiation strategy	Conservative strategy		Early initiation strategy	Conservative strategy	
	$n = 403$	$n = 692$		$n = 390$	$n = 390$	
Age, years	80.00 (69.00–87.00)	83.00 (75.00–89.00)	0.329	81.00 (70.25–87.00)	81.00 (70.00–87.00)	0.014
Female	150 (37.2)	281 (40.6)	0.069	148 (37.9)	152 (39.0)	0.021
BMI, kg/m^2	22.04 (19.80–24.82)	21.65 (19.40–23.81)	0.193	21.89 (19.74–24.66)	22.03 (19.98–24.28)	0.033
Alb, g/dL	3.50 (3.20–3.80)	3.40 (3.00–3.70)	0.280	3.50 (3.19–3.80)	3.50 (3.10–3.80)	0.015
AST, U/L	33.00 (23.00–61.00)	32.00 (22.00–57.00)	0.102	33.00 (23.00–61.00)	33.05 (22.00–65.00)	0.077
ALT, U/L	25.00 (15.00–50.50)	22.00 (13.00–44.25)	0.020	25.00 (15.00–50.00)	25.00 (15.00–51.00)	0.018
GGT, U/L	48.00 (25.00–90.00)	40.04 (22.00–68.31)	0.233	47.00 (24.00–89.26)	43.00 (23.00–70.00)	0.176
Total bilirubin, mg/dL	1.00 (0.69–1.42)	0.90 (0.60–1.30)	0.171	1.00 (0.66–1.40)	1.00 (0.70–1.45)	0.015
NT-proBNP, pg/mL	7786.25 (4592.50–11 525.50)	8393.68 (4660.00–12 334.51)	0.066	7812.81 (4572.17–11 695.00)	8135.71 (4722.34–11 843.77)	0.018
Sodium, mEq/L	140.00 (136.37–142.00)	140.00 (137.00–142.00)	0.002	140.00 (136.19–142.00)	140.00 (137.00–142.00)	0.003
Potassium, mEq/L	4.30 (3.90–4.70)	4.30 (3.80–4.70)	0.035	4.30 (3.90–4.70)	4.30 (3.80–4.70)	0.006
CRP, mg/dL	1.05 (0.42–2.70)	1.49 (0.45–4.22)	0.205	1.05 (0.40–2.68)	1.29 (0.38–3.66)	0.139
CK, U/L	112.00 (71.00–198.50)	117.89 (69.00–216.00)	0.083	112.00 (71.00–196.45)	128.86 (73.00–249.75)	0.130
LDH, U/L	279.00 (236.88–361.50)	295.00 (242.00–379.84)	0.072	280.26 (237.25–361.75)	296.51 (244.83–386.85)	0.056
BUN, mg/dL	27.50 (19.35–40.60)	28.85 (20.00–44.00)	0.031	27.70 (19.52–41.15)	27.85 (19.45–43.75)	0.014
eGFR, mL/min/1.73 m^2	40.01 (24.69–55.81)	39.85 (24.80–56.12)	0.006	39.74 (24.38–55.60)	41.22 (24.52–55.74)	0.020
WBC, $10^3/\mu L$	7330.00 (5700.00–9255.00)	7265.00 (5640.00–9812.50)	0.081	7255.72 (5700.00–9230.00)	7315.00 (5757.50–9900.00)	0.129
Hb, g/dL	12.20 (10.60–14.00)	11.50 (10.00–13.30)	0.264	12.10 (10.50–13.70)	12.10 (10.50–13.80)	0.006
Plt, $10^3/\mu L$	18.10 (14.15–23.35)	18.20 (13.80–23.80)	0.009	17.90 (14.10–23.20)	18.40 (13.93–23.78)	0.051
Smoking	177 (43.9)	264 (38.2)	0.118	170 (43.6)	169 (43.3)	0.005
Blood pressure, mmHg						
<100	49 (12.2)	83 (12.0)	0.005	47 (12.1)	50 (12.8)	0.024
100–140	259 (64.3)	419 (60.5)	0.078	248 (63.6)	242 (62.1)	0.032
>140	95 (23.6)	190 (27.5)	0.091	95 (24.4)	98 (25.1)	0.018
Use of IV diuretics on Day 0	271 (67.2)	472 (68.2)	0.021	261 (66.9)	260 (66.7)	0.005
Use of IV vasodilators on Day 0	132 (32.8)	208 (30.1)	0.058	128 (32.8)	119 (30.5)	0.050
Use of the arterial line on Day 0	33 (8.2)	61 (8.8)	0.022	33 (8.5)	40 (10.3)	0.062

Values are presented in median (interquartile range) or *n* (%).
Alb, albumin; ALT, alanine aminotransferase; ASMD, absolute standardized mean difference; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CK, creatinine kinase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; Hb, haemoglobin; IV, intravenous; LDH, lactate dehydrogenase; NT-proBNP, N-terminal pro-brain natriuretic peptide; WBC, white blood cell.

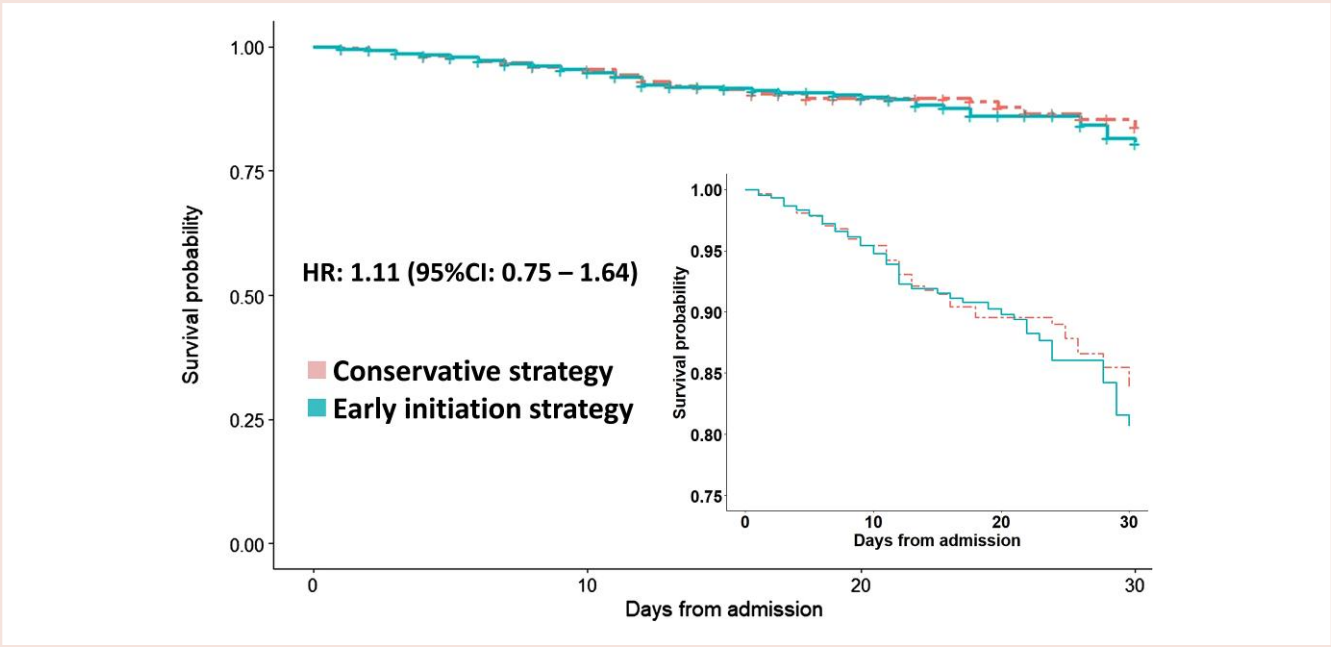


Figure 2 Association between treatment strategies and all-cause death. Early initiation strategy: initiating beta-blockers with continuing dobutamine during the grace period (7 days). Conservative strategy: refraining from initiating beta-blockers during the grace period if the patient was using dobutamine. All participants were cloned into two replicates, and each replicate was assigned to each strategy at the start of the follow-up. The replicates were artificially censored when they deviated from the assigned strategy. Survival curves were weighted with the inverse probability of treatment assignment and the inverse probability of artificial censoring. The hazard ratio and its 95% confidence interval were estimated on all-cause death with a Cox proportional hazard model. CI, confidence interval; HR, hazard ratio.

Table 2 Sensitivity analysis for different grace periods

Estimates	Main analysis	Grace period: 5 days from admission	Grace period: 9 days from admission
HR	1.11 (0.75–1.64)	1.05 (0.70–1.59)	1.02 (0.72–1.45)
Mortality, %, early initiation strategy	19.3 (10.6–30.7)	17.4 (8.6–29.1)	19.4 (11.6–30.0)
Mortality, %, conservative strategy	16.2 (9.2–25.3)	16.6 (8.8–25.3)	17.7 (9.6–26.8)
RMST, days, early initiation strategy	27.7 (26.3–28.6)	27.5 (26.1–28.7)	27.4 (26.3–28.3)
RMST, days, conservative strategy	27.8 (26.6–28.8)	27.6 (26.4–28.7)	27.3 (26.1–28.5)

The 95% CIs are provided in parentheses. Grace periods were used to define clinical strategies. The early initiation strategy was defined as initiating beta-blockers with continuing dobutamine during the grace period. Conservative strategy was defined as refraining from initiating beta-blockers during the grace period if the patient was under dobutamine. Survival curves for the two sensitivity analyses are displayed in Supplementary material online, *Figure S3*.
CI, confidence interval; HR, hazard ratio; RMST, restricted mean survival time.

of the follow-up, the hazard ratio was 1.07 (0.74–1.53). The estimated 60-day mortality and RMST also suggested a slightly worse survival rate in the early initiation strategy than in the conservative strategy (see Supplementary material online, *Figure S5*).

When we did not apply IPTW and IPCW (i.e. leaving selection bias), the result slightly moved towards the direction of favouring the early initiation strategy [hazard ratio: 0.96 (0.66–1.41)] compared with the main analysis. Similarly, when we did not apply cloning, censoring, and IPCW (i.e. leaving immortal time bias), the early initiation strategy showed better survival rates than the conservative strategy [hazard ratio: 0.79 (0.52–1.20); *Table 3*]. In this sensitivity analysis, the survival curve of the early initiation strategy was nearly flat in the first few days, suggesting the influence of immortal time bias (see Supplementary material online, *Figure S6*).

Discussion

In the present observational study, explicitly designed to emulate a pragmatic RCT, beta-blocker initiation under dobutamine infusion within 7 days from admission was not associated with either an increase or decrease in all-cause mortality (*Graphical abstract*). The result was consistent across several sensitivity analyses, and additional analyses highlighted the importance of adjusting for selection bias and immortal time bias in observational studies in case patient selection preceded the treatment assignment, even in studies on acute-stage care.

Our findings extend the current state of knowledge about the prompt initiation of beta-blockers in advanced heart failure. Although previous reports suggested that baseline beta-blocker use did not influence clinical outcomes in patients with cardiogenic shock treated by

Table 3 Additional analysis with incomplete emulations

Methods/estimates	Main analysis	Leaving selection bias[a]	Leaving immortal time bias[b]
IPTW	✓		✓
Cloning and artificial censoring	✓	✓	
IPCW	✓		
HR	1.11 (0.75–1.64)	0.96 (0.66–1.41)	0.79 (0.52–1.20)
Mortality, %, early initiation strategy	19.3 (10.6–30.7)	17.9 (10.2–27.5)	17.0 (12.2–22.6)
Mortality, %, conservative strategy	16.2 (9.2–25.3)	17.2 (10.3–26.6)	18.1 (13.1–23.0)
RMST, days, early initiation strategy	27.7 (26.3–28.6)	27.8 (26.6–28.6)	28.0 (27.4–28.6)
RMST, days, conservative strategy	27.8 (26.6–28.8)	27.6 (26.4–28.5)	27.3 (26.6–28.0)

The 95% CIs are provided in parentheses. Survival curves for the two sensitivity analyses are displayed in Supplementary material online, *Figure S5*.
CI, confidence interval; HR, hazard ratio; IPCW, inverse probability of censoring weight; IPTW, inverse probability of treatment weight; RMST, restricted mean survival time.
[a]In this sensitivity analysis, the main analysis was repeated without IPTW and IPCW. The 30-day mortality and RMST, and their 95% confidence intervals, were estimated using unweighted Kaplan-Meirer curve and non-parametric bootstrap with 1000 samples.The hazard ratio was estimated with a unweighted Cox proportional hazard model adjusting the same covariates as the main analysis.
[b]In this sensitivity analysis, the main analysis was repeated without cloning and artificial censoring. The treatment assignment was determined based on the eventual clinical course of each patient. The 30-day mortality and RMST, and their 95% confidence intervals, were estimated using Kaplan-Meirer curve with IPTW and non-parametric bootstrap with 1000 samples. The hazard ratio was estimated with the Cox proportional hazard model with IPTW adjusting the same covariates as the main analysis.

dobutamine,[30] no evidence, guidelines, or physiological rationale have supported the initiation of beta-blockers under dobutamine infusion, which was occasionally conducted in a real-world scenario.[8–12] Our results indicate no significant positive or negative effect of such beta-blocker use on survival. A sensitivity analysis, which estimated all-cause mortality in a 60-day follow-up scenario, showed consistent results, suggesting that long-term benefits may not justify the early initiation of beta-blockers under dobutamine infusion.

Our study also emphasized the importance of accounting for immortal time bias and selection bias, which have often been ignored in observational studies. Immortal time bias arose and favoured the early initiation strategy when study arms were defined primitively with propensity-score matching on eventual clinical courses. Selection bias was also confirmed to favour the early initiation strategy when IPTW and IPCW were not implemented. Given that patients who were eventually initiated beta-blockers were likely to have only a mild clinical status, we observed the directions of bias as expected. These findings indicate that failing to adjust for these biases would overestimate the effect of beta-blocker initiation on survival outcomes in patients with advanced heart failure.

While conducting an RCT immediately is practically difficult, an observational study with an explicit emulation of a target trial would be one of the best possible alternatives. Because we utilized the diagnosis procedure combination database, which is based on electronic health records, the application of claims data would be complementary to our study. Claims data would provide implications from a long-term perspective as they can help follow up patients from inpatient to outpatient settings across facilities, identify medical histories, and increase the cohort size. On the other hand, claims data are disadvantaged in terms of reflecting patients' health status, especially with regard to the results of various examinations. The attempt to integrate electronic health records and claims data may leverage the strength of both databases, although practical difficulties lie in linking data from multiple providers.[31]

Several limitations should be considered in this study. First, there is the likelihood of the presence of unmeasured or unrecorded confounders, including aetiology of heart failure, baseline heart rhythm, heart rate, ejection fraction, lactic acid, or socioeconomic status. The null result limited the assessment of the robustness of the findings regarding these confounders with established methods. Second, the study did not account for other inotropes because the prevalence rate of milrinone use was very low (<1.0%) in our cohort, and levosimendan was not approved in Japan. Third, since the database covers only inpatient care, it lacks a longitudinal follow-up across inpatient and outpatient care. Fourth, there remains a possibility of misclassifications in administrative data, particularly with regard to blood pressure, because its recorded timing has ambiguity (i.e. at patient encounters or care unit admissions). Fifth, because our cohort excluded patients with extreme background characteristics to consider initiating beta-blockers, it is uncertain whether our results can be applied to patients with severer clinical statuses. Sixth, although a subgroup analysis showed no obvious difference in the results between bisoprolol and carvedilol, uncertainty remains regarding the impact of beta-1 selectivity. Last, the study did not account for the dosing of beta-blockers during dobutamine infusion, which may affect clinical outcomes. These limitations and null results in the present study support conducting future RCTs on this topic.

Conclusions

In this observational study with a multicentre inpatient-care database emulating an RCT for patients with advanced heart failure, we did not observe either a decreased or increased risk of all-cause mortality through the initiation of beta-blockers during dobutamine infusion. The study was carefully designed to mitigate immortal time bias and selection bias. Although there is still room for individualized discussions and our findings need to be validated in other settings, the initiation of beta-blockers under dobutamine infusion may not generally be recommended in the management of advanced heart failure.

Lead author biography

Yuichiro Mori, MD, Master of Public Health (MPH), is a PhD candidate at the Graduate School of Medicine, Kyoto University in Kyoto, Japan. He is a certified interventional cardiologist in Japan and has pursued an MPH degree from the Johns Hopkins Bloomberg School of Public Health, concentrating in health systems and policy. His current research focuses on applying causal inference methods in the field of heart failure, especially in prevention, to support evidence-based decision-making by policymakers.

Data availability

The statistical code is available from the corresponding author upon reasonable request. The data sets generated and/or analysed during the current study are not publicly available due to the confidentiality contract with the data provider. A minimum data set to replicate the statistical analysis could be shared with the data provider's permission, which the corresponding author can request in response to reasonable inquiries.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Authors' contribution

Y.M. conceptualized the study and wrote the draft. All authors contributed to the design and conduct of the study; interpretation of the data; and preparation, review, or approval of the manuscript.

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