Supplementary Materials: Effects of Widespread Inotrope Use in Acute Heart Failure Patients

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1. Supplementary Methods.

In-hospital mortalities and the causes of death were adjudicated by an independent event committee. This adjudication form was referenced by the adjudication of death of typical 3-phase randomized control trials such as RELAX and RELAX-AHF-2 trial. The Definition of the Causes of Death are as follows:

1. Death due to Heart failure (HF) progression: Death occurring in the context of clinically worsening symptoms and/or signs of heart failure. New or worsening signs and/or symptoms of congestive HF may include any of the following:
   - New or increasing symptoms and/or signs of HF requiring the initiation of, or an increase in, treatment directed at HF or occurring in a patient already receiving maximal therapy for HF
   - HF symptoms or signs requiring continuous intravenous therapy or oxygen administration
   - Cardiogenic shock, manifested as clinical signs and symptoms of hypoperfusion felt to be secondary to cardiac dysfunction, and not occurring in the context of an acute myocardial infarction or as the consequence of a primary arrhythmic event
   Patients who are hospitalized and are being actively treated for HF and who have an arrhythmia as the terminal event will be classified as having a HF-related death.

2. Sudden cardiac death: Death that occurs unexpectedly in a previously stable patient will be adjudicated as being sudden cardiac death. The death can be further categorized as witnessed or unwitnessed:

   Witnessed sudden cardiac death:
   - Witnessed within 60 minutes of the onset of new or worsening cardiac symptoms
   - Witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording or witnessed on a monitor by either a medic or paramedic)
   - Subjects unsuccessfully resuscitated from cardiac arrest or successfully resuscitated from cardiac arrest but who die without identification of a non-cardiac etiology
   Note that if a witnessed sudden cardiac death occurs as a complication of another primary cardiac process, eg, cardiogenic shock or acute myocardial infarction, the primary process should be adjudicated as the cause of death.

   Unwitnessed sudden cardiac death:
   - An unwitnessed death is one that occurs in a patient who when last seen alive within an observation period of 72 hours:
     - Did not manifest another life-threatening non-cardiac disease (e.g., infectious, metabolic disorders); and/or
     - Did not reveal a cause other than cardiovascular (e.g., trauma) at the scene of death; and/or
     - Death was ruled cardiovascular in cause on an autopsy report or death certificate, and occurred in the absence of pre-existing circulatory failure or other modes of death.

3. Death due to Acute Coronary Syndrome: Death occurring up to 14 days after a d
ocumented acute coronary syndrome and/or acute myocardial infarction and where there is no conclusive evidence of another cause of death. If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence.

4. **Death due to Cerebrovascular Event**: Death occurring up to 30 days after a suspected or confirmed stroke (ischemic stroke or hemorrhagic stroke) based on clinical signs and symptoms as well as neuroimaging and/or autopsy, and where there is no conclusive evidence of another cause of death.

5. **Death due to Other Cardiovascular Causes**: Death must be due to a documented cardiovascular cause not included in the above categories (e.g., peripheral vascular disease, systemic embolus, pulmonary embolism, cardiac procedure complication, and so on)

6. **Death due to Non-Cardiovascular cause**: Non-cardiovascular death is defined as any death not covered by cardiac death or vascular death

2. **Supplementary Tables**

**Table S1.** Specific diseases entity of the main underlying etiology of acute heart failure, ischemic heart disease.

| Ischemic heart disease* | Total population (n = 2096) |
|-------------------------|-----------------------------|
| Ischemic cardiomyopathy | 650 (31.0%)                 |
| Acute coronary syndrome | 1202 (57.3%)                |
| -STEMI                   | 382 (18.2%)                 |
| -NSTEMI                  | 578 (27.6%)                 |
| -Unstable Angina         | 244 (11.6%)                 |
| -Miscellaneous           | 242 (11.5%)                 |

* Ischemic heart disease was defined as a proven coronary artery stenosis that can clinically explain the pathophysiology of heart failure, with no other plausible explanation.

**Table S2.** Concomitant medications of the total population.

| Medication during admission | Total population (n = 5471) | Inotrope users (n = 1703) | Inotrope non-users (n = 3768) | p value |
|-----------------------------|----------------------------|--------------------------|-----------------------------|---------|
| ACE inhibitors              | 2119 (38.7%)               | 696 (40.9%)              | 1423 (37.8%)                | 0.029   |
| ARB                         | 2972 (54.3%)               | 1017 (59.7%)             | 1955 (51.9%)                | <0.001  |
| Statin                      | 2549 (46.6%)               | 827 (48.6%)              | 1722 (45.7%)                | 0.050   |
| Beta blocker                | 2271 (41.5%)               | 830 (48.7%)              | 1441 (38.2%)                | <0.001  |
| Ivabradine                  | 6 (0.1%)                   | 5 (0.3%)                 | 1 (<0.1%)                  | 0.013   |
| Oral nitrate                | 3100 (56.7%)               | 1092 (64.1%)             | 2008 (53.3%)                | <0.001  |
| Loop diuretics              | 5007 (91.5%)               | 1614 (94.8%)             | 3393 (90.0%)                | <0.001  |
| Thiazides                   | 748 (13.7%)                | 280 (16.4%)              | 468 (12.4%)                 | <0.001  |
| Amiodarone                  | 846 (15.5%)                | 497 (29.2%)              | 349 (9.3%)                  | <0.001  |
| Digoxin                     | 1836 (33.6%)               | 663 (38.9%)              | 1173 (31.1%)                | <0.001  |
| Aspirin                     | 3560 (65.1%)               | 1131 (66.4%)             | 2429 (64.5%)                | 0.162   |
| Warfarin                    | 1713 (31.3%)               | 536 (31.5%)              | 1177 (31.2%)                | 0.861   |
| Heparin                     | 2543 (46.5%)               | 1033 (60.7%)             | 1510 (40.1%)                | <0.001  |
| IV vasodilators             | 2270 (41.5%)               | 844 (49.6%)              | 1426 (37.8%)                | <0.001  |
Table S3. Prescription pattern of inotropes in inotrope users (n = 1703).

| Inotrope users (n = 1703) | Inotrope users (n = 1703) |
|--------------------------|--------------------------|
| Dopamine                 | 961 (56.4%)              |
| Dobutamine               | 1245 (73.1%)             |
| Norepinephrine           | 521 (30.6%)              |
| Milrinone                | 133 (7.8%)               |
| Number of Inotropic agent per patient | 1.68 ± 0.88 |
| -Single inotropic agent  | 942 (55.3%)              |
| -Combination of inotropic agents | 761 (44.7%) |

Table S4. Multivariate analysis for predictors of in hospital adverse outcomes by subgroup analysis.

| Low Initial SBP (< 90 mmHg) | Normal Initial SBP (≥ 90 mmHg) |
|-----------------------------|-------------------------------|
| OR 95% CI p                 | OR 95% CI p                   |
| Old age (> 70 years old)    | 2.886 1.840–4.528 <0.001      |
| Low BMI (< 25 kg/m²)        | 1.807 1.099–2.973 0.020       |
| Chronic renal failure       | 2.762 1.547–4.929 0.001       |
| Uric Acid >7 mg/dL          | 1.604 1.095–2.348 0.015       |
| High CRP                    | 2.675 1.665–4.297 <0.001      |
| Low LVEF (< 40%)            | 1.737 1.093–2.760 0.020       |
| Renal Replacement therapy   | 13.572 3.648–50.497 <0.001    |
| Inotrope usage              | 2.694 0.548–13.258 0.223      |
| HFrEF (LVEF ≤ 40%)          | 6.364–9.104 <0.001            |
| HFpEF (LVEF ≥50%)           | 5.931 3.864–9.104 <0.001      |

SBP, systolic blood pressure; HFrEF, heart failure with preserved ejection fraction; HFpEF, heart failure with reduced ejection fraction; OR, odds ratio; HR, Hazard ratio; CRP, C-reactive protein; BMI, body mass index; LVEF, left ventricular ejection fraction.
Table S5. Post-discharge medications.

| Post-Discharge Medication | Inotrope Users (n = 1402) | Inotrope Non-Users (n = 3635) | p Value |
|---------------------------|---------------------------|-------------------------------|---------|
| ACE inhibitors            | 369 (30.1%)               | 1011 (32.5%)                  | 0.127   |
| ARB                       | 444 (36.2%)               | 1559 (50.1%)                  | <0.001  |
| Statin                    | 592 (48.3%)               | 1469 (47.2%)                  | 0.526   |
| Beta blocker              | 643 (52.4%)               | 2001 (64.3%)                  | <0.001  |
| Ivabradine                | 5 (0.4%)                  | 4 (0.1%)                      | 0.129   |
| Oral nitrate              | 257 (21.0%)               | 747 (24.0%)                   | 0.032   |
| Loop diuretics            | 875 (71.4%)               | 2424 (77.9%)                  | <0.001  |
| Statin                    | 161 (13.1%)               | 374 (12.0%)                   | 0.317   |
| Amiodarone                | 128 (10.4%)               | 199 (6.4%)                    | <0.001  |
| Digoxin                   | 355 (29.0%)               | 881 (28.3%)                   | 0.676   |
| Aspirin                   | 694 (56.6%)               | 1789 (57.5%)                  | 0.590   |
| Warfarin                  | 391 (31.9%)               | 1005 (32.3%)                  | 0.794   |

ACE, Angiotensin-converting enzyme; ARB, Angiotensin receptor blocker.

Table S6. Multivariate analysis for predictors of post-discharge 1-month mortality by subgroup analysis.

| Low Initial SBP (< 90 mmHg) | Normal Initial SBP (≥ 90 mmHg) |
|-----------------------------|---------------------------------|
| HR                          | 95% CI                          | p     | HR                          | 95% CI                          | p     |
| Old age (> 70 years old)    | 11.091                          | 1.910–64.397                     | 0.007 | 3.600                         | 0.953–13.599                | 0.059 |
| Hyponatremia                | -                               | -                               | -    | 2.753                         | 1.015–7.471                 | 0.047 |
| Renal Replacement therapy   | 24.114                          | 2.763–210.481                   | 0.004 | 2.165                         | 1.147–4.090                 | 0.017 |
| Inotrope usage              | 0.644                           | 0.110–3.752                     | 0.624 | 3.584                         | 1.280–10.037                | 0.015 |

SBP, systolic blood pressure; LV, left ventricle; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; OR, odds ratio; HR, Hazard ratio.

Table S7. Baseline characteristics of patients presenting with low vs normal initial SBP in the propensity score matched cohort.

| Low initial SBP (< 90 mmHg) | Normal initial SBP (≥ 90 mmHg) | p value |
|-----------------------------|---------------------------------|---------|
| (n = 114)                   | (n = 1864)                      |         |
| Sex (male)                  | 61 (53.5%)                      | 1088 (58.4%) | 0.307 |
| Age (years old)             | 63.6±15.0                       | 66.6±14.8 | 0.034 |
| BMI (kg/m\(^2\))            | 22.3±3.6                        | 23.2±3.7 | 0.015 |
| LVEF (%)                    | 33.5±14.0                       | 33.8±14.6 | 0.871 |
| Risk factors                |                                 |         |
| HTN, n (%)                  | 36 (31.6%)                      | 1047 (56.2%) | <0.001 |
| DM, n (%)                   | 25 (21.9%)                      | 715 (38.4%) | <0.001 |
| Smoking, %*                 | 21.9/24.6/35.5                  | 19.5 / 21.3 / 59.2 | 0.482 |
| Previous MI, n (%)          | 18 (15.8%)                      | 309 (16.6%) | 0.826 |
| Previous PCI, n (%)         | 17 (14.9%)                      | 331 (17.8%) | 0.439 |
| Previous CABG, n (%)        | 9 (7.9%)                        | 123 (6.6%) | 0.590 |
| COPD, n (%)                 | 10 (8.8%)                       | 198 (10.6%) | 0.532 |
| CRF, n (%)                  | 13 (11.4%)                      | 257 (13.8%) | 0.472 |
Initial SBP: $79\pm10$ vs $133\pm28$, $<0.001$
Initial DBP: $51\pm9$ vs $80\pm18$, $<0.001$
Initial HR: $86\pm29$ vs $94\pm24$, 0.006
Valve disease, n (%): 10 (8.8%) vs 300 (16.1%), 0.037
Previous CVA, n (%): 21 (18.4%) vs 259 (13.9%), 0.179
Atrial fibrillation, n (%): 83 (72.8%) vs 1375 (73.8%), 0.821

Laboratory analysis:
- WBC (10^9/L): $9230\pm4430$ vs $8820\pm3890$, 0.337
- Hb (g/dL): $12.2\pm2.7$ vs $12.5\pm2.3$, 0.141
- Platelet (10^9/L): $210\pm78$ vs $209\pm87$, 0.995
- Na (mEq/L): $136\pm5$ vs $137\pm5$, 0.010
- Uric acid (mg/dL): $7.7\pm3.2$ vs $7.1\pm3.2$, 0.055
- Creatinine (mg/dL): $2.69\pm3.70$ vs $2.43\pm4.28$, 0.537

Clinical events:
- In-hospital adverse outcomes: 9.6% (11/114) vs 4.6% (86/1864), 0.016
- 1 month mortality: 1.9% (2/104) vs 3.5% (62/1791), 0.398

BMI, body mass index; LVEF, left ventricular ejection fraction; HTN, hypertension; DM, diabetes mellitus; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; CVA, cerebrovascular accident; WBC, white blood cell; Hb, hemoglobin; Na; sodium; BUN, blood urea nitrogen; CRP, C-reactive protein; BUN, brain natriuretic peptide; NTproBNP, n-terminal Brain natriuretic peptide. * smoking: current smoker / ex- smoker / never smoker.

**Table S8.** Characteristics and outcomes after strict propensity score matching.

| Inotrope Users (n = 238) | Inotrope Non-Users (n = 238) | SMD | p Value |
|---------------------------|------------------------------|-----|--------|
| **Age (years old)**      | 68.8 (13.5)                  | 69.1 (13.0) | 0.017 | 0.85 |
| **BMI (kg/m²)**           | 23.4 (3.9)                   | 23.6 (3.9)  | 0.043 | 0.64 |
| Initial SBP (mmHg)        | 132.1 (30.9)                 | 136.0 (29.3) | 0.129 | 0.16 |
| Initial DBP (mmHg)        | 76.1 (18.5)                  | 78.9 (19.3) | 0.148 | 0.11 |
| Initial HR (bpm)          | 95.3 (23.8)                  | 96.1 (23.8) | 0.032 | 0.73 |
| BSA (m²)                  | 1.7 (0.2)                    | 1.7 (0.2)   | 0.010 | 0.91 |
| Pulse (beat/minute)       | 95.3 (23.8)                  | 96.1 (23.8) | 0.032 | 0.73 |
| LVEF (%)                  | 33.5 (13.9)                  | 34.5 (14.5) | 0.069 | 0.45 |
| **Laboratory analysis**   |                              |              |       |      |
| CK-MB                     | 12.4 (28.7)                  | 8.6 (20.2)   | 0.152 | 0.10 |
| WBC (10^9/L)              | 9,576.6 (4,487.7)            | 9,235.2 (3,662.9) | 0.083 | 0.36 |
| Hb (g/dL)                 | 12.4 (2.4)                   | 12.4 (2.2)   | 0.021 | 0.82 |
| Platelet (10^9/L)         | 217.3 (87.2)                 | 224.7 (78.7) | 0.089 | 0.33 |
| Na (mEq/L)                | 137.8 (4.6)                  | 137.8 (4.5) | 0.015 | 0.87 |
| K (mEq/L)                 | 4.4 (0.7)                    | 4.4 (0.7)    | 0.033 | 0.72 |
| Uric acid (mg/dL)         | 7.4 (2.7)                    | 6.9 (3.9)    | 0.132 | 0.15 |
| Creatinine (mg/dL)        | 1.5 (1.5)                    | 1.4 (1.3)    | 0.043 | 0.64 |
| Glucose (mg/dL)           | 182.6 (93.6)                 | 179.8 (86.9) | 0.031 | 0.74 |
| RDW (%)                   | 14.6 (2.3)                   | 14.4 (1.8)   | 0.097 | 0.29 |
| HbA1C (%)                 | 6.7 (1.3)                    | 6.8 (1.3)    | 0.051 | 0.58 |
| Total cholesterol (mg/dL) | 161.7 (44.6)                 | 162.8 (45.0) | 0.024 | 0.79 |
| TG (mg/dL)                | 102.8 (74.2)                 | 105.5 (66.1) | 0.037 | 0.68 |
| HDL (mg/dL)               | 39.1 (14.5)                  | 40.5 (12.8) | 0.097 | 0.29 |
| Albumin (g/dL)            | 3.6 (0.5)                    | 3.7 (0.5)    | 0.113 | 0.22 |
| BUN (mg/dL)               | 25.2 (15.3)                  | 27.7 (16.9) | 0.155 | 0.09 |
| cTNI (ng/mL)              | 2.8 (7.6)                    | 2.0 (8.2)    | 0.104 | 0.26 |
| CRP (mg/L)                | 2.8 (4.8)                    | 2.4 (3.9)    | 0.090 | 0.33 |

| N (%) | N (%) | SMD | p |
|-------|-------|-----|---|
| Sex (male) | 140 (58.8) | 136 (57.1) | 0.034 | 0.78 |
| HTN    | 155 (65.1) | 157 (66.0) | 0.018 | 0.92 |
| DM     | 126 (52.9) | 131 (55.0) | 0.042 | 0.71 |
| Current smoking | 64 (26.9) | 57 (23.9) | 0.116 | 0.45 |
| Previous MI | 37 (15.5) | 41 (17.2) | 0.045 | 0.71 |
### Table 1. Baseline Characteristics of Participants

| Characteristic          | User Group | Non-User Group | p-value |
|-------------------------|------------|----------------|---------|
| Previous PCI            | 44 (18.5)  | 37 (15.5)      | 0.078   |
| Previous CABG           | 10 (4.2)   | 12 (5.0)       | 0.040   |
| COPD                    | 30 (12.6)  | 24 (10.1)      | 0.080   |
| CRF                     | 28 (11.8)  | 27 (11.3)      | 0.013   |
| Valve disease           | 30 (12.6)  | 20 (8.4)       | 0.137   |
| Previous CVA            | 32 (13.4)  | 36 (15.1)      | 0.048   |
| Atrial fibrillation     | 45 (18.9)  | 50 (21.0)      | 0.053   |
| NYHA IV                 | 153 (64.3) | 153 (64.3)     | 0.082   |
| Renal transplantation   | 11 (4.6)   | 19 (8.0)       | 0.139   |
| Vasodilator medication  | 63 (26.5)  | 52 (21.8)      | 0.108   |
| BNP ≥ 500 or NTproBNP ≥ 1000 (pg/mL) | 199 (83.6) | 200 (84.0) | 0.011   |

### 3. Supplementary Figure

#### Figure S1.
Detailed cause of in-hospital clinical events.

In-hospital clinical events occurred in 280 (5.1%) of the cases during admission. Cardiac death occupied the majority of in-hospital clinical events (70.3%), and the most common cause of cardiac death was HF aggravation (60.4%). In subgroup analysis, cardiac death was more common in inotrope users (45.3% [24/53] vs 76.2% [173/227], p < 0.001), while non-cardiovascular death events were more common in inotrope non-users (24.5% [13/53] vs 13.7% [31/227], p = 0.050). All 8 cases (4.1%) of sudden cardiac death events occurred in inotrope users.