Predictors of In-hospital Mortality in Cardiogenic Shock Patients on Vasoactive or Inotropic Support

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ABSTRACT

BACKGROUND: Though controversial, the short-duration in-patient use of inotropes in cardiogenic shock (CS) remain an ACC/AHA Class IIa indication, and are frequently used in the initial treatment of CS. We evaluated in-patient mortality and effect on mortality risk of commonly used vasoactive inotropic medications for the medical management of SCAI stage B and C cardiogenic shock patients in a tertiary care cardiac care unit: dobutamine, dopamine, milrinone, and norepinephrine.

METHODS: We retrospectively evaluated 342 patients who received dobutamine, milrinone, dopamine, norepinephrine or a combination of these medications for SCAI stage B and C cardiogenic shock. Cox proportional hazards were used to form longitudinal mortality predictions.

RESULTS: Overall in-patient mortality was 18%. Each 1 µg/kg/minute increase in dobutamine independently corresponded to a 15% increase in risk of mortality. High dose dobutamine >3µg/kg/minute was associated with 3-fold increased risk compared to <3µg/kg/minute (P<.001). Use of milrinone, norepinephrine, and dopamine were not independently associated with mortality.

CONCLUSION: We demonstrate that the overall in-hospital mortality of SCAI stage B and C cardiogenic shock patients medically managed on inotropes was not in excess of prior studies. Dobutamine was independently associated with mortality, while other vasoactive inotropic medications were not. Inotropes remain a feasible method of managing SCAI stage B and C cardiogenic shock.

KEYWORDS: Cardiogenic shock, vasoactive inotropic score, in-hospital mortality

Key Points
1. SCAI stage B and C patients on dobutamine have a 15% increased risk of mortality per each 1 µg/kg/minute increase in dobutamine.
2. Higher doses of combined inotropes (measured by the VIS) and dobutamine >3µg/kg/minute are associated with 3-fold increased risk of mortality in cardiogenic shock.
3. Milrinone, Norepinephrine, and Dopamine were not significantly associated with mortality in this population.

Introduction/Background

The inpatient use of inotropes in acute decompensated heart failure (ADHF) and cardiogenic shock (CS) remains controversial. There is a paucity of randomized control trials for placebo versus dobutamine or milrinone in patients with cardiogenic shock. Studies examining the use of inpatient inotropes have yielded mixed results. Inpatient inotropic support has been associated with worsening arrhythmias and worse mortality due to arrhythmias.1 Milrinone was studied in a randomized, placebo-controlled trial and found to have an increase in hypotension and new atrial arrhythmias, but did not differ in in-patient or 60-day mortality.2 However, inotropes have been shown to improve other important metrics for heart failure, including reducing length of stay and symptomatic improvement while awaiting left ventricular assist devices or heart transplant.3,4 Also, a small placebo-controlled study demonstrated survival benefit of dobutamine and amiodarone compared to those on amiodarone alone.5,6

For patients who have contraindications to mechanical circulatory support (MCS) or present at a site without those indications for inotropes are as bridge therapy until definitive therapy such as coronary revascularization, MCS, or heart transplantation can occur to preserve end-organ performance. Inotropes also have a class IIa indication as longer-term therapy as bridge to transplant or left ventricular assist device and a
Hypothesis and Purpose
We sought to define in-patient mortality and predictors of mort-
ality in a contemporary cohort of patients presenting with ADHF
and CS requiring low dose inotropic medications at our center.

Methods
This observational study was a retrospective analysis of patients
admitted to Loma Linda University Medical Center who were
diagnosed with cardiogenic shock as coded by ICD-10 code
R57.0 or ICD-9 code 785.51, and then evaluated for risk of in-
hospital mortality using a retrospective longitudinal analysis.

Data was collected for patients who satisfied inclusion criteria
that consisted of all adults (≥18 years of age) who presented
with cardiogenic shock and were admitted to the cardiac care
unit and received inotropic and/or vasoactive pressor support
between January 2015 and December 2018. Patients were
excluded if they were on home inotropic support or received
mechanical circulatory support. Key data collected were demo-
graphic baseline characteristics (age, gender, race, weight), rea-
son for admission (ADHF, acute coronary syndrome [ACS], or
other), length of stay, left ventricular ejection fraction (LVEF),
comorbidities (hypertension, hyperlipidemia, diabetes, coronary
artery disease [CAD], etiology of heart failure), blood pressure
and heart rate at the time of inotropic or vasoactive drip initia-
tion, time-averaged doses and duration of intravenous vasoac-
tive or inotropic therapy, acute hypoxic respiratory failure
(AHRF) (requiring 2 L oxygen or more), acute liver injury
(ALI) (elevation of ALT > 10× upper limit of normal, INR > 2.0 in patients not on warfarin), or bilirubin (> 3 mg/dL)
and acute kidney injury (AKI) (> 0.3 mg/dL increase in serum
creatinine within the 3 months prior to admission, or lowest
serum creatinine noted during hospitalization). The clinical
endpoint evaluated was inpatient mortality.

Vasoactive and inotropic medication doses were time-
averaged: duration of each dose was multiplied by the con-
centration for that time, so the µg/kg per person was
calculated for each patient
(dopamine dose (mg/kg/min) + dobutamine dose (mg/kg/min) +
100 × epinephrine dose (mg/kg/min) + 10 × milrinone dose (mg/
kg/min) + 10,000 × vasopressin dose (mg/kg/min) + 100 ×
norepinephrine dose (mg/kg/min)). The clinical endpoint
was inpatient mortality documented in the electronic
health record. SCAI cardiogenic shock stages were assigned
retrospectively using admission data based on presence of
hypotension, tachycardia, elevated lactate, end-organ dys-
function and refractory shock, as there were very few cases
in which invasive hemodynamics were performed. In this
data, all therapeutic regimens, including choice of ino-
trropic or vasoactive medication captured in this study, were
based on clinician judgment rather than a study protocol.

The Loma Linda University Institutional Review Board
approved the data collection protocol used in this study.

We compared baseline characteristics stratified by survival
in this analysis. Baseline characteristics are described as
mean ± SD for continuous variables and number (proportion)
for categorical variables. These variables were compared using
F-test, t-test, or fisher exact test, or chi-square test as appropri-
ate. Cox proportional hazards were adjusted for age, gender,
race, history of hypertension, presence of AKI, AHRF, or ALI
on admission, admission lactate, and SCAI stage. The aver-
age doses of all inotropes or vasoactive medications were
treated as continuous variables. Low-dose dobutamine was defined as
≤3 µg/kg/minute, and high-dose dobutamine was defined as
doses ≥ 3 µg/kg/minute. Three Cox proportional hazards
regressions were used. In the first, we analyzed the average dose
of each inotrope or vasoactive medication in addition to the
risk factors listed above to determine the contribution of each
inotrope on mortality risk. In the second and third, we explored
the significance of a high dose versus low dose of dobutamine
in the setting of an overall vasoactive or inotropic medication
load by using the VIS score. The second cox regression com-
pares dobutamine doses ≤3, 3 to 6, and >6 µg/kg/minute to
those who were not on dobutamine (but were on other ino-
tropes, as represented by VIS), which established the linearity
of the mortality risk of dobutamine. The third compares those
with an average dobutamine dose of ≤3 µg/kg/minute to those
with an average dobutamine dose of >3 µg/kg/minute to com-
pare low dose to high dose dobutamine. Missing data were
omitted. R version 3.6.1 was used for all statistical analysis
(The R Foundation for Statistical Computing, Vienna, Austria).

Results
During the study period, 342 patients meeting inclusion crite-
ria were identified. The baseline characteristics of the cohort
stratified by survival group are summarized in Table 1, with
combinations of inotropes in Supplemental Figure 1. There
were no statistically significant differences between the 2
groups, except for end-organ damage at presentation, reason
for admission, lactate, and SCAI stage.

Vital signs, time-averaged vasoactive and inotropic medica-
tions, and admission lactate levels summarized according to
survival group in Table 2. In univariate analysis, the cohort that
survived had an average lower heart rate (84 vs 93 beats per
Table 1. Basic characteristics of the study population, stratified by survival status.

|                          | TOTAL (N = 342) | SURVIVED (N = 279) | DIED (N = 63) | P VALUE |
|--------------------------|-----------------|--------------------|---------------|---------|
|                          | MEAN ± SD OR # (%) | MEAN ± SD OR # (%) | MEAN ± SD OR # (%) |         |
| Gender                   | .8              |                    |               |         |
| Men                      | 226 (66)       | 183 (65.6)         | 43 (68.2)     |         |
| Women                    | 116 (34)       | 96 (33.4)          | 20 (31.7)     |         |
| Race                     | .39             |                    |               |         |
| Caucasian                | 139 (40.6)     | 112 (40.1)         | 27 (42.9)     |         |
| Hispanic                 | 127 (37.1)     | 100 (35.8)         | 27 (42.9)     |         |
| Black                    | 40 (11.7)      | 35 (12.5)          | 5 (7.9)       |         |
| Other                    | 36 (10.5)      | 32 (11.5)          | 4 (6.3)       |         |
| Age (years)              | 63.4 ± 15.2    | 67 ± 14.8          | .54           |         |
| Reason for admission     | <.001           |                    |               |         |
| ADHF                     | 225 (65.8)     | 200 (71.7)         | 25 (39.7)     |         |
| ACS                      | 77 (22.5)      | 45 (16.1)          | 32 (50.8)     |         |
| Other                    | 40 (11.7)      | 34 (12.2)          | 6 (9.5)       |         |
| LVEF (%)                 | 23.2 ± 15.4    | 23 ± 15.4          | 23.7 ± 15.3   | .79     |
| Heart failure etiology†  | .31             |                    |               |         |
| Ischemic                 | 175 (51.8)     | 137 (50)           | 38 (60.3)     |         |
| Non-ischemic             | 130 (38.5)     | 112 (40.1)         | 18 (28.6)     |         |
| Combined                 | 32 (9.5)       | 25 (9.1)           | 7 (11.1)      |         |
| Comorbidities            |                |                    |               |         |
| HTN                      | 229 (67)       | 194 (69.5)         | 35 (55.5)     | .05     |
| HLD                      | 158 (46.2)     | 125 (44.8)         | 33 (52.4)     | .34     |
| DM                       | 152 (44.4)     | 120 (43)           | 32 (50.8)     | .32     |
| CAD                      | 188 (55)       | 147 (52.7)         | 41 (65.1)     | .10     |
| Valvular disease         | 87 (25.4)      | 79 (28.3)          | 8 (12.7)      | .015    |
| ESRD                     | 16 (4.7)       | 11 (3.9)           | 5 (7.9)       | .3      |
| COPD                     | 42 (12.3)      | 34 (12.2)          | 8 (12.7)      | 1       |
| OSA                      | 19 (5.6)       | 18 (6.5)           | 1 (1.6)       | .22     |
| Methamphetamine abuse    | 41 (12)        | 36 (12.9)          | 5 (7.9)       | .48     |
| Afib/flutter              | 131 (38.3)     | 109 (39.1)         | 22 (34.9)     | .64     |
| ICD                      | 77 (22.5)      | 66 (23.7)          | 11 (17.5)     | .37     |
| CRT                      | 32 (9.4)       | 28 (10.3)          | 4 (6.3)       | .50     |
| SCAI stage               | <.001           |                    |               |         |
| B                        | 96 (28.7)      | 95 (34.1)          | 3 (4.8)       |         |
| C                        | 241 (70.5)     | 181 (64.9)         | 60 (95.2)     |         |

(Continued)
### Table 2. Inotrope and pressor dosing, and associated vitals, stratified by survival status.

|                              | TOTAL (N=342) | SURVIVED (N=279) | DIED (N=63) | P VALUE |
|------------------------------|---------------|-------------------|-------------|---------|
|                              | MEAN ± SD OR # (%) | MEAN ± SD OR # (%) | MEAN ± SD OR # (%) | MEAN ± SD OR # (%) |
| **End-organ damage**         |               |                   |             |         |
| AKI                          | 223 (65)      | 171 (61)          | 52 (82.5)   | .002    |
| ALI                          | 62 (28)       | 62 (22)           | 34 (54)     | <.001   |
| AHRF                         | 175 (51)      | 127 (45)          | 48 (76)     | <.001   |
| **Length of stay (days)**    | 8.5 ± 15.4    | 8.8 ± 6.6         | 7 ± 8.8     | .12     |

**Abbreviations:** ADHF, acute decompensated heart failure; ACS, acute coronary syndrome; Afib/flutter, atrial fibrillation or atrial flutter; AHFR, acute hypoxic respiratory failure; AKI, acute kidney injury; ALI, acute liver injury; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DM, diabetes mellitus; ESRD, end stage renal disease; HLD, hyperlipidemia; HTN, hypertension; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; OSA, obstructive sleep apnea.

*Data available for 274 in the survived group, 337 in the total cohort.

*Fisher-exact test used, and groups 3 and 4 collapsed into 1 in analysis.

### Table 1. (Continued)

|                              | TOTAL (N=342) | SURVIVED (N=279) | DIED (N=63) | P VALUE |
|------------------------------|---------------|-------------------|-------------|---------|
|                              | MEAN ± SD OR # (%) | MEAN ± SD OR # (%) | MEAN ± SD OR # (%) | MEAN ± SD OR # (%) |
| HR inotrope started (BPM)    | 86 ± 19       | 84 ± 19           | 93 ± 21     | .002    |
| SBP inotrope started (mmHg)  | 100.4 ± 20.7  | 102 ± 20          | 93 ± 20     | .002    |
| DBP inotrope started (mmHg)  | 65.4 ± 15.6   | 66 ± 16           | 62 ± 15     | .04     |
| HR max inotrope (BPM)        | 90.6 ± 20.5   | 88.5 ± 19         | 99.9 ± 24.1 | <.001   |
| SBP max inotrope (mmHg)      | 105.5 ± 22.1  | 108.4 ± 20        | 92.4 ± 25.9 | <.001   |
| DBP max inotrope (mmHg)      | 65.1 ± 17.2   | 67 ± 16           | 56 ± 17.9   | <.001   |
| Dobutamine (yes/no)          | 256 (74.9)    | 201 (72)          | 55 (87)     | .02     |
| Milrinone (yes/no)           | 70 (20.5)     | 62 (22)           | 8 (12.7)    | .14     |
| Norepinephrine (yes/no)      | 61 (17.8)     | 36 (12.9)         | 25 (39.6)   | <.001   |
| Dopamine (yes/no)            | 109 (31.9)    | 86 (31)           | 23 (36.5)   | .4      |
| Dobutamine dose (µg/kg/min)  | 3.7 ± 2.4     | 3.2 ± 1.8         | 5.4 ± 3.3   | <.001   |
| Milrinone dose (µg/kg/min)   | 0.27 ± 0.1    | 0.26 ± 0.08       | 0.35 ± 0.19 | .21     |
| Norepinephrine dose (µg/kg/min) | 0.15 ± 0.16 | 0.11 ± 0.13   | 0.22 ± 0.16 | .008    |
| Dopamine dose (µg/kg/min)    | 4.6 ± 3.8     | 3.7 ± 2.7         | 8 ± 5       | <.001   |
| VIS                          | 7.5 ± 11.1    | 5.4 ± 7.4         | 16.8 ± 18   | <.001†  |
| Number of patients on 1 VI med | 220 (64.3) | 188 (67.4)       | 22 (34.9)   |         |
| Number of patients on 2 VI med | 112 (32.7) | 78 (28)          | 34 (54)     |         |
| Number of patients on 3 VI med | 18 (5.3)  | 11 (3.9)         | 7 (11)      |         |
| Number of patients on 4 VI med | 2 (0.6)    | 2 (0.7)          | 0 (0)       |         |
| Admission lactate (mmol/L)*  | 4.1 ± 3.6     | 3.4 ± 2.8         | 6.7 ± 5.1   | <.001   |

**Abbreviations:** BPM, beats per minute; HR, heart rate; mmHg, millimeters of mercury; SBP, systolic blood pressure; VI, vasoactive or inotropic; VIS, vasoactive inotropic score.

*Data available for 274 in the survived group, 337 in the total cohort.

*Fisher-exact test used, and groups 3 and 4 collapsed into 1 in analysis.
minute), and a higher initial systolic (102 vs 93 mmHg), higher diastolic blood pressure (66 vs 62 mmHg), and lower lactate (3.4 vs 6.7 mmol/L) as compared to those who died. These differences were more pronounced at peak doses of vasoactive and inotropic drips (Supplemental Table 2, Supplemental Figure 2). Time-averaged doses were lower in the survivors as compared to those who died: average dobutamine was 3.2 µg/kg/minute versus 5.4 µg/kg/minute, average milrinone dose was 0.26 µg/kg/minute versus 0.35 µg/kg/minute, average norepinephrine dose was 0.11 µg/kg/minute versus 0.22 µg/kg/minute, and the average dopamine dose was 3.7 µg/kg/minute versus 8 µg/kg/minute. Overall, the cohort was predominantly SCAI stage C (70%), though amongst those who died, there were 95% SCAI stage C. A summary of combinations of inotropes used in the study can be found in Supplemental Figure 1. The mortality rate with dobutamine alone was 15% (n = 137), milrinone alone was 3% (n = 35), dopamine alone was 4% (n = 24), and norepinephrine alone 18% (n = 13).

In this cohort of predominantly SCAI Stage B and C cardiogenic shock patients on inotropic or vasoactive medications who did not undergo mechanical support, the overall mortality rate was 18%. In patients on low-dose dobutamine, and in the lowest quintile of the VIS, the mortality was 9% (Supplemental Tables 2 and 3). A summary of the multivariable cox proportional hazards results are presented in Table 3. When adjusting for the doses of other inotropes, SCAI stage, presence of end-organ dysfunction, lactate, and other common risk factors, only dobutamine was significantly associated with a 15% increased risk in mortality with each 1 µg/kg/minute increase in dose. Milrinone, norepinephrine, and dopamine were not significantly associated with mortality in the same multivariable cox regression. When high-dose dobutamine (>3 µg/kg/minute) was compared to low-dose dobutamine (<3 µg/kg/min), adjusting for use of other inotropes using the VIS, those on high-dose dobutamine are at nearly 3-fold increased risk of mortality (P < .001) (Table 3). The risk of mortality of dobutamine was found to be non-linear, with no increased risk at low doses (Table 3). Moreover, the statistical model, given the adjustment for total inotrope dose, actually tested the predictive ability of dobutamine in comparison to “equivalent” doses of other inotropes, holding the total inotrope load constant.

Discussion
In this retrospective analysis of real world SCAI stage B and C cardiogenic shock patients at a single tertiary care academic center, we demonstrate that low doses of inotropes can be used in the initial medical management cardiogenic shock without excess mortality.14 We also report lower doses of inotropes than used in previous studies where the vasoactive/inotrope dosing data is available, and provide in detail the combinations of vasoactive or inotropic medications.15

Our data would also suggest that for patients with cardiogenic shock stage B or C, the mortality of low-dose inotropes is approximately 9%. However, the mortality rate significantly increases as the dose of inotropes increases. This would suggest that for patients with SCAI stage B and C cardiogenic shock, low-dose inotropes may not be as deleterious as previously thought as an initial strategy. However, if higher doses are required to maintain hemodynamic and perfusion parameters, then more invasive strategies should be considered in those who are candidates for mechanical circulatory support.

The inpatient mortality of cardiogenic shock has been reported to be between about 12% to 37% recent major studies.13,15,16 Similar to these groups, our cohort is a heterogenous group, with a 66% with ADHF complicated by cardiogenic shock, while 22.5% had ACS complicated by cardiogenic shock. The ADHERE registry had patients with ADHF of whom 8% were on inotropic support, though no data was

| Table 3. Results of multivariate analyses. | HAZARD RATIO | LOWER 95% CI | UPPER 95% CI | P-VALUE |
|-------------------------------------------|--------------|--------------|--------------|--------|
| Milrinone dose*                           | 1.12         | 0.08         | 14.9         | .93    |
| Dobutamine dose*                          | 1.15         | 1.05         | 1.3          | .002   |
| Norepinephrine dose*                      | 2.0          | 0.26         | 16.3         | .50    |
| Dopamine dose*                            | 0.97         | 0.90         | 1.06         | .54    |
| Dobutamine <3 µg/kg/min*                  | 0.68         | 0.29         | 1.63         | .38    |
| Dobutamine 3-6 µg/kg/min*                 | 1.77         | 0.78         | 4.0          | .17    |
| Dobutamine >6 µg/kg/min*                  | 4.83         | 1.77         | 13.2         | .002   |
| High dose dobutamine (>3 µg/kg/min)*†     | 2.85         | 1.58         | 5.14         | <.001  |

*Corrected for age, gender, race, lactate, hypertension, SCAI score, acute kidney injury, acute liver injury, acute hypoxic respiratory failure, dobutamine, dopamine, milrinone, dopamin.

†Corrected for age, gender, race, lactate, hypertension, SCAI score, acute kidney injury, acute liver injury, acute hypoxic respiratory failure, vasoactive inotropic score, and compared to low-dose dobutamine (<3 µg/kg/minute).
published on use of dopamine or norepinephrine within this registry. Mortality associated with patients only on milrinone or only on dobutamine were 12% to 14% respectively. Our cohort demonstrated a 3% mortality rate on milrinone alone, and 13% mortality rate on dobutamine alone (Supplemental Figure 1). However, there are 2 crucial differences to be noted between our cohort and the ADHERE HF patients who were on inotropic support, these being average systolic blood pressure and use of multiple vasoactive or inotropic medications. Only 2% of the patients in the ADHERE registry were hypotensive, but 8% received inotropic or vasoactive medications. In our cohort of SCAI stage B and C cardiogenic shock patients, the average systolic blood pressure when dobutamine or milrinone was initiated was 99 and 108 mmHg respectively, lower than that of the patients in the ADHERE registry (about 120 mmHg).15,16

In the ALARM-HF trial, the mortality of those receiving IV inotropes was 25.9%, with a 1.5-fold increase in mortality for patients on dopamine or dobutamine, and a >2.5-fold increase in mortality for those on norepinephrine or epinephrine. Notably, the average dose of dobutamine was 10 µg/kg/minute, the average dose of norepinephrine used was 0.8 µg/kg/minute, and the average dose of dopamine was 3 µg/kg/minute. While our study used significantly lower doses of dobutamine and norepinephrine than ALARM-HF reported, we did use higher doses of dopamine (Table 2). Our study does demonstrate that patients on dobutamine doses >3 µg/kg/minute, as well as higher scores on the VIS were associated with increased risk of mortality, when corrected for measures of disease severity such as presence of end-organ dysfunction, lactate, and SCAI stage. However, contrary to the results of ALARM-HF and ADHERE, milrinone, dopamine, and norepinephrine did not have a statistically significant increase in mortality risk.

The CardShock trial had a significantly lower overall systolic blood pressure (78 mmHg) reported than the ALARM-HF or ADHERE trials, or than our cohort, and had an overall mortality rate of 37%. Similarly, a small, randomized control trial evaluating the use of IABP versus inotropes in cardiogenic shock (n = 32) demonstrated a significant improvement in the blood pressure, and pulmonary capillary wedge pressure in the IABP group compared with the inotrope group, however no significant difference in in-hospital mortality. Den Uil et al used relatively low doses of inotropes, similar to our cohort (though they used enoximone whereas we used milrinone as a phosphodiesterase 3 inhibitor). Unfortunately, CardShock did not report the doses of inotropes or vasoactive medications used in order to compare to our cohort.

We addressed combinations of inotropes by using the vasoactive inotropic score, which has been validated in pediatric and adult populations. The VIS was developed originally in pediatric cardiogenic shock and post-surgical patients as a way of measuring the cumulative effect of multiple vasoactive or inotropic medications on 1 patient, though originally developed in pediatric patients, has recently been validated in an adult cardiogenic shock patient population. This prior analysis by Na et al grouped the VIS scores to demonstrate higher mortality rate by VIS both when grouped and as a continuous variable. Interestingly, the VIS was not significantly associated with mortality when dobutamine doses greater than 3 µg/kg/minute were administered. Confounding factors for using dobutamine including AKI on admission or hypotension were corrected for both indirectly with SCAI staging and directly with a categorical variable.

This study had several limitations. It is a single-center study, so prescribing biases in dosing and choice of inotropic or vasoactive medication may not represent that of other trials. It is difficult to elucidate clear differences between vasoactive inotropic medication groups as there were a significant portion of patients who were on multiple medications, though correction with VIS attempted to account for this. We also had limited data from right heart catheterizations, so SCAI classifications, which were proposed after this study was completed, were based on non-invasive measures such as end organ dysfunction, lactate, systolic blood pressure rather than invasive hemodynamics. Additionally, we measured in-patient mortality rather than 30 or 60 day mortality, which may attribute to the overall lower rate of mortality. As this was an observational study, the conclusions drawn here are hypothesis generating and need evaluation in prospective randomized trials. However, such a trial would be difficult to design, as the development of a true control group of patients not treated with vasoactive or inotropic medications for cardiogenic shock would not be ethical.

Conclusion

This paper demonstrates that low-dose inotropes remain a high-risk but acceptable method of initially managing cardiogenic shock. The use of dobutamine at higher doses is independently associated with mortality in a contemporary patient population of SCAI stage C and B cardiogenic shock when correcting for the presence of other inotropes in 2 separate models. Treating the CS population remains a significant challenge, requiring further prospective randomized trials which may specify optimal doses and combinations of vasoactive inotropic medications. Given the broad spectrum of patients presenting with cardiogenic shock, practitioners need further clarification on the least harmful initial medical management of cardiogenic shock, and when a patient should be supported with MCS rather than vasoactive inotropic medications alone. Further areas of inquiry include management of CS with vasoactive inotropic support and invasive hemodynamics to better assess at what doses or combined vasoactive inotropic escalation to MCS should be considered to improve overall mortality in CS.
Author Contributions
All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Dr. Gary Fraser and Dr. Shuktika Nandkeolyar. The first draft of the manuscript was written by Dr. Shuktika Nandkeolyar and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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

Ethics
This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of Loma Linda University Medical Center approved this study.

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Supplemental Material
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