# Health Outcomes with and without Use of Inotropic Therapy in Cardiac Surgery

## *Results of a Propensity Score–matched Analysis*

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CME This article has been selected for the Anesthesiology CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

## ABSTRACT

**Background:** Inotropes used to obtain short-term hemodynamic benefits in cardiac surgery may carry a risk of increased myocardial ischemia and adverse outcomes. This study investigated the association between intra- and postoperative use of inotropes and mortality and postoperative complications.

**Methods:** A historic cohort study using prospective data from the Western Denmark Heart Registry on 6,005 consecutive cardiac surgery cases from three university hospitals. Propensity matching on pre- and intraoperative variables was used to identify a subgroup of patients receiving inotropic therapy (n = 1,170) *versus* comparable nonreceivers (n = 1,170) for outcome analysis.

**Results:** Two thousand ninety-seven patients (35%) received inotropic therapy; 3,908 (65%) did not receive any inotropic or vasopressor support perioperatively. Among propensity-matched cohort including 2,340 patients 30-day mortality was 3.2% and 1-yr mortality was 7.6%. In the matched cohort, patients exposed to inotropes had a higher 30-day mortality (adjusted hazards ratio, 3.7; 95% CI, 2.1 to 6.5) as well as a higher 1-yr mortality rate (adjusted hazards ratio, 2.5; 95% CI, 1.8 to 3.5) compared with nonreceivers. Among propensity-matched, the following absolute events rates were observed: myocardial infarction 2.4%, stroke 2.8%, arrhythmia 35%, and renal replacement therapy 23.9%. Inotropic therapy was independently associated with postoperative myocardial infarction (adjusted odds ratio, 2.1; 95% CI, 1.4 to 3.0), stroke (adjusted odds ratio, 2.4; 95% CI, 1.4 to 4.3), and renal replacement therapy (adjusted odds ratio, 7.9; 95% CI, 3.8 to 16.4).

**Conclusion:** Use of intra- and postoperative inotropes was associated with increased mortality and major postoperative morbidity. **(Anesthesiology 2014; 120:1098-108)**

LOW cardiac output syndrome is a common complication in cardiac surgery patients[1] and inotropic support is frequently initiated to improve postbypass ventricular function. Inotropes may improve hemodynamics, but there is a potential risk for increased myocardial oxygen consumption resulting in cardiac ischemia and potential damage of hibernating but viable myocardium, particularly in patients with ischemic heart disease. The clinical efficacy of perioperative inotropes has been assessed in randomized clinical trials primarily in relation to hemodynamic endpoints. Most previous randomized trials have not been powered to study the efficacy in relation to "hard" clinical outcomes, including cardiac morbidity and mortality.[2] Use of inotropes has been associated with adverse clinical outcomes in a few observational studies[3–5]: In a sentinel study by Fellahi *et al.*,[3] use of dobutamine was associated with increased postoperative morbidity.

### What We Already Know about This Topic

- Previous studies have suggested that inotropic therapy after cardiac surgery may be associated with increased morbidity but the impact of these drugs on overall survival is unknown.

### What This Article Tells Us That Is New

- In an observational study of 6,005 patients using propensity score matching, perioperative use of inotropes was independently associated with increased 1-yr mortality (adjusted hazard ratio of 2.5). The results indicate that the beneficial effects of current inotropic drugs may be limited to only short-term hemodynamic improvement in patients after cardiac surgery.

However, the study sample was too small to investigate mortality, and the association between inotrope exposure and short- and long-term mortality thus remained unclear. At present, there is only limited data to guide practice patterns

This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page 1067.

Submitted for publication January 10, 2013. Accepted for publication January 22, 2014. From the Department of Anesthesiology and Intensive Care (D.V.N., C.-J.J.) and Department of Clinical Epidemiology (M.K.H., S.P.J.), Aarhus University Hospital, Aarhus, Denmark; Department of Anesthesia and Intensive Care, Odense University Hospital, Odense, Denmark (M.H.); and Department of Anesthesia and Intensive Care, Aalborg University Hospital, Aalborg, Denmark (K.H.).

and evidence-based use of inotropes in cardiac surgery. This has resulted in an ongoing debate on the value or harm associated with use of inotropes in cardiac surgery.[6] Thus, clinical practice in inotrope management is highly dependent on the individual center and physician preferences.[7–10]

The aim of the current study was to investigate whether use of inotropes was associated with short- and long-term mortality and an increased incidence of postoperative complications such as myocardial infarction (MI), stroke, arrhythmia, and renal failure in patients undergoing cardiac surgery. To obtain a sufficient sample size to investigate the association between perioperative inotropic therapy and these rare adverse clinical outcomes, a historical cohort study was conducted using data from a population-based clinical cardiac registry. A propensity score–matched analysis was used to minimize the risk of selection bias and confounding.

## Materials and Methods

### Patient Population

This study was a multicenter, historical cohort study involving 6,005 consecutive adult patients undergoing cardiac surgery with or without cardiopulmonary bypass (CPB) at three Danish university cardiac centers (Odense University Hospital, Aarhus University Hospital, and Aalborg University Hospital) from April 1, 2006 to December 31, 2009. Patients met the following inclusion criteria: Coronary artery bypass grafting (CABG) or CABG with valve surgery or combined with other procedures or surgery involving the thoracic aorta. Patients were excluded if they had undergone procedures only offered at one of the participating cardiac centers such as heart transplantation, pulmonary thrombendarterectomy, or percutaneous valve replacement. Patients dying during surgery and patients regarded inoperable after sternotomy were excluded. Patients who underwent more than one cardiac surgical procedure during the study period were included with only the first surgical procedure to ensure independency. In case of missing data on procedure type, CPB, or exposure to inotropes patients were excluded (fig. 1).

Study start was determined as the time when data on inotrope treatment were included in the clinical registry from which data were obtained.

The study period was not determined by a formal power calculation; however, our study population was large compared with previous studies and the statistical precision of the risk estimates was reasonable. The study was approved by the Danish Data Protection Agency, Copenhagen, Denmark, and had institutional approval from Aarhus University Hospital, Aarhus, Denmark, Odense University Hospital, Odense, Denmark, and Aalbor University Hospital, Aalborg, Denmark.

### Western Denmark Heart Registry

Data were obtained from the Western Denmark Heart Registry (WDHR). Registration is mandatory and Internet-based and completed perioperatively by the surgeon and attending anesthesiologist. The registry includes detailed information on patient history, type of procedure, intra- and postoperative management including inotropic therapy and in-hospital complications. The registry provides the Danish Heart Registry (DHR) with data on all consecutive patients undergoing cardiac surgery in the western part of Denmark. Data quality is ensured using automatic validation rules at data entry combined with systematic validation procedures and random spot-checks of data after entry. Coverage of the DHR is routinely evaluated by comparing with data from the Danish National Patient Register including data on all procedures performed in both private and public hospitals in Denmark. These analyses have shown a high coverage of the DHR, with greater than 95% reporting of all CABG procedures.[11] Random samples of the data reported to the DHR from WDHR have been validated against the local patient files (both electronic and paper files). The main finding was that the data in the WDHR were correct with $\kappa$ values between 0.91 to 1 (DHR—Annual Report 2007, University of Southern Denmark: The Board of Danish Heart Registry and National Institute of Public Health, 2008), but there was a high proportion of missing data especially concerning patient history and late complications.[11] Missing data have been retrieved later from local patient files (both electronic and paper) and overall missing data constituted less than 0.3 and 0% for outcome data. The WDHR has proven a valuable data source in research, providing ongoing longitudinal registration of detailed data on patients and procedures.[12]

### Perioperative Management

All preoperative cardiac medication was continued until the morning of surgery except for angiotensin-converting enzyme inhibitors, aspirin, and thrombocyte function inhibitors. β-Blocking agents were continued on the day of surgery in chronically treated patients. All patients received standard premedication in the form of a benzodiazepine 60 to 90 min before surgery. Cardiac centers B: Standard total intravenous anesthesia using propofol 40 to 80 μg/kg/min, sufentanil 3 to 5 μg/kg, and pancuronium. Cardiac centers A and C: anesthesia induction with midazolam or pentobarbital together with fentanyl 0.01 to 0.025 mg/kg or sufentanil 3 to 5 μg/kg, and rocuronium/cisatracurium. Anesthesia was maintained with sevoflurane 1.5 to 2.5% during ventilation.

In the operating room, patients were routinely monitored including five-lead electrocardiography, radial, pulse oximetry, capnography, and temperature monitoring. Most patients were monitored using pulmonary artery catheters with or without continuous cardiac output measurement (Swan Ganz CCO/VIP; Edwards Lifesciences LLC, Irvine, CA). Most patients were additionally monitored with transesophageal echocardiography. Routine surgical and cardio-protective strategies were used in most patients at all centers. There were minor differences between the centers regarding primary cardioplegia. Center B used crystalloid cardioplegia, center C used blood-cardioplegia, and center A used either combined blood and crystalloid cardioplegia or standard crystalloid cardioplegia. Standard techniques with closed CPB

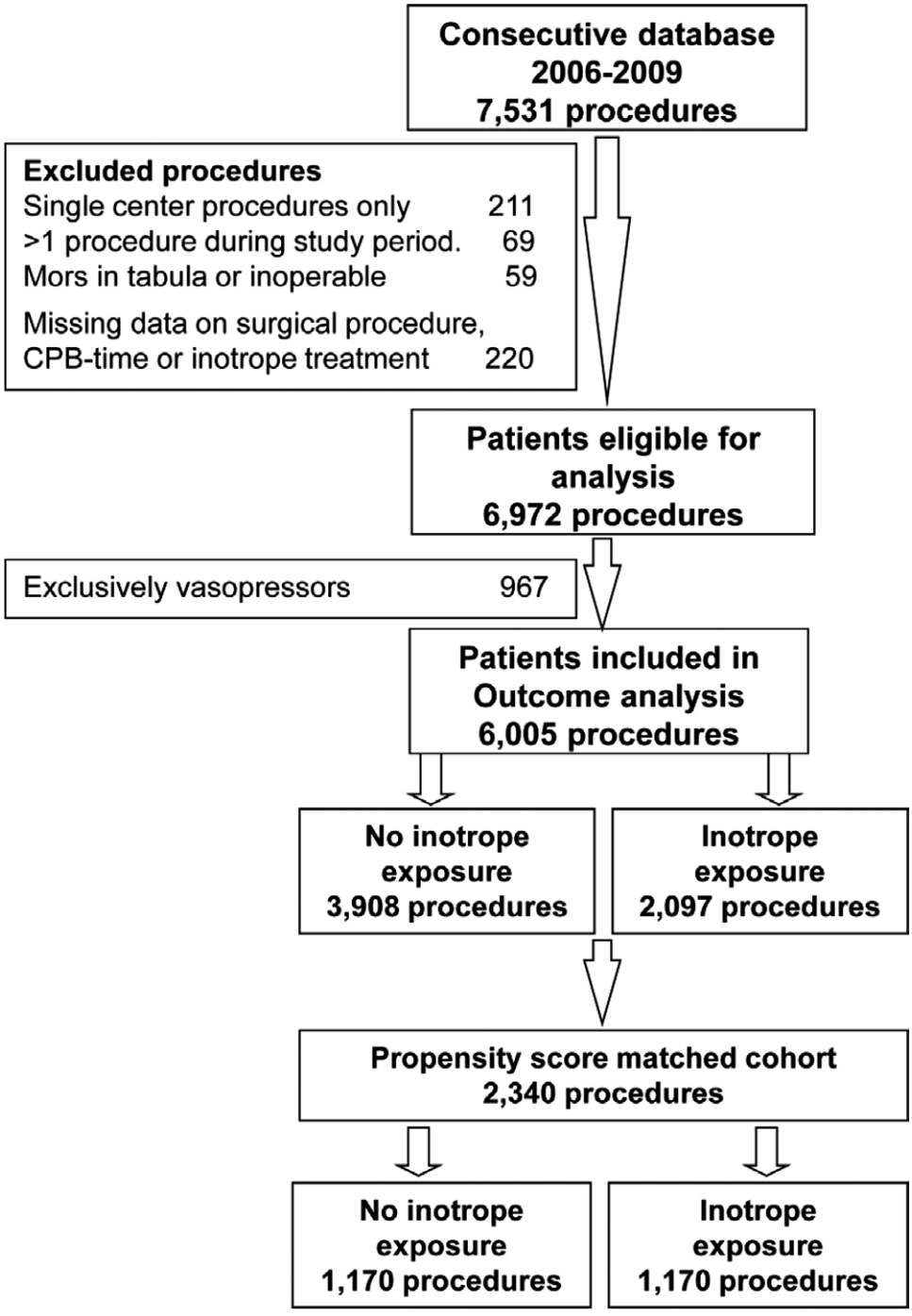


**Fig. 1.** Flowchart of included and excluded procedures in the study cohort. CPB = cardiopulmonary bypass.

systems, consisting of tubing with a surface-modifying additive coating, an arterial filter with heparin coating, a hollow fiber membrane oxygenator with a surface-modified additive coating, and a venous and cardiotomy reservoir were standard procedures for patients on CPB. Most patients were maintained normothermic or slightly hypothermic. At the end of the surgical procedure, reperfusion of the heart was performed on an individual basis according to the patient's general condition and time on cross clamp. Use of calcium at termination of CPB was at the discretion of the attending anesthesiologist. There was no fixed postoperative treatment regimen for either pharmaceutical or mechanical support.

### *Inotropic Therapy*

Neither institutional guidelines nor prespecified algorithms dictating inotropic support during separation from CPB or stay in the intensive care unit (ICU) were used in the participating cardiac centers.

Consequently, the perioperative use and discontinuation of inotropic use was at the discretion of the attending anesthesiologist. In Denmark, the anesthesiologist is responsible for the ICU and immediate postoperative care and the same doctors who perform the anesthesia generally conduct postoperative observation and treatment. Inotropic therapy was defined as any dose of infusion of inotropes for more than 1 h administered peroperatively and/or postoperatively in the ICU. The following inotropes were used as perioperative therapy: milrinone, dobutamine, dopamine, epinephrine, and levosimendan. Patients who exclusively received norepinephrine, the only vasopressor used in the cohort, were excluded, whereas patients who did not receive perioperative inotropic therapy served as a reference group ("No inotropes"). The perioperative period was defined as time from induction of anesthesia until discharge from the ICU.

### Provider-related Characteristics

An attending anesthesiologist and a responsible surgeon were registered for each patient. The database could only identify the anesthesiologists and surgeons performing the intraoperative part of the procedures. Providers were divided into three groups based on at least one third of total cases in the high and moderate groups: Anesthesiologists: high: greater than 40 cases per year; medium: 16 to 40 cases per year; low: 15 cases per year or less. For surgeons: high: greater than 65 cases per year; medium: 46 to 65 cases per year; low: 45 cases per year or less.

### Patient- and Procedure-related Characteristics

The additive EuroSCORE 1 characterized patients. Three subscores were created based on known EuroSCORE variables to characterize patients more accurately: EuroSCORE comorbidity score consisted of scores on chronic pulmonary disease, extracardiac arteriopathy, neurological dysfunction, previous cardiac surgery, serum creatinine greater than 200 μmol/l, and active endocarditis.

EuroSCORE cardiac condition score consisted of unstable angina, recent MI, pulmonary hypertension, and critical preoperative state. EuroSCORE procedure score consisted of emergency surgery, procedures other than isolated CABG, operation on thoracic aorta, and postinfarct septal rupture. Information on preoperative arrhythmia and preoperative renal replacement therapy (RRT) was included in the analysis as covariates. CPB was grouped as CPB time 120 min or less or bypass time greater than 120 min or off pump. Anesthetic techniques were expressed as intravenous anesthesia, inhalational anesthesia, and epidural analgesia.

### Clinical Outcomes

The primary clinical outcome was long-term mortality measured as 1 yr postoperative mortality. We used the unique civil registration number assigned to all Danish citizens[13] to link data across registers. Date of death was obtained through the Civil Registration System where the exact date of death of each citizen is registered. All patients in the study cohort had at least 1-yr follow-up. Secondary clinical outcomes were 30-day mortality and major postoperative in-hospital complications including MI, postoperative arrhythmia, postoperative stroke, and postoperative RRT documented in the WDHR before hospital discharge.

Twelve-lead electrocardiogram recordings were routinely assessed by experienced physicians immediately after arrival in the ICU, postoperatively, and on the morning of the first postoperative day. After referral to the surgical ward, electrocardiogram recordings were assessed if patients developed clinical signs of MI: In case of signs of MI (newly develop Q wave) or creatine kinase-MB greater than 100 mmol/l, a cardiologist would be consulted. MI would be registered as an event in WDHR if diagnosed by a cardiologist. The diagnosis would in most cases be supported by assessments from echocardiography and/or percutaneous coronary arteriography. Postoperative arrhythmia was defined as verified episodes of ventricular tachycardia, ventricular fibrillation, and/or atrial fibrillation. Postoperative stroke was defined as a postoperative cerebral vascular event with transient or permanent neurological deficit. Postoperative RRT was defined as hemodialysis, continuous veno-venous filtration, or peritoneal dialysis initiated postoperatively.

### Statistical Analysis

Study results are presented as median (interquartile range) or numbers (%) where appropriate. Longitudinal data were analyzed using Mann–Whitney test and categorical with chi-square test for unmatched data. *P* value less than 0.05 was considered statistically significant. Inotropic therapy use was not randomly assigned in the study population, thus we used propensity score matching to reduce the risk of bias due to confounding.[14,15] Matching was done using 5-1 digit matching (Greedy method). Each patient receiving inotropic therapy was matched to one nonreceiver with a similar propensity score. The propensity score was based on the following covariates: sex, age, chronic pulmonary disease, extracardiac arteriopathy, neurologic dysfunction disease, previous cardiac surgery, serum creatinine greater than 200 μmol/l, active endocarditis, critical preoperative state, preoperative arrhythmia, preoperative RRT, unstable angina, recent MI, pulmonary hypertension, left ventricular ejction fraction 30% or less, emergency surgery, CABG, thoracic aortic surgery, postinfarct septal rupture, intravenous anesthesia, epidural supplement, CPB time greater than 120 min, off-pump surgery, and cardiac center; 39.8% were matched on five digits, 8.1% on four digits, 19.3% on three digits, 23.3% on two digits, and 9.4% on one digit. An absolute standardized difference less than 10% was considered to support the assumption of balance between the groups[16,17] (fig. 2). The variables included in the propensity score model were selected among available baseline variables based on known associations between inotropic therapy and/or study outcomes. The model was not specified according

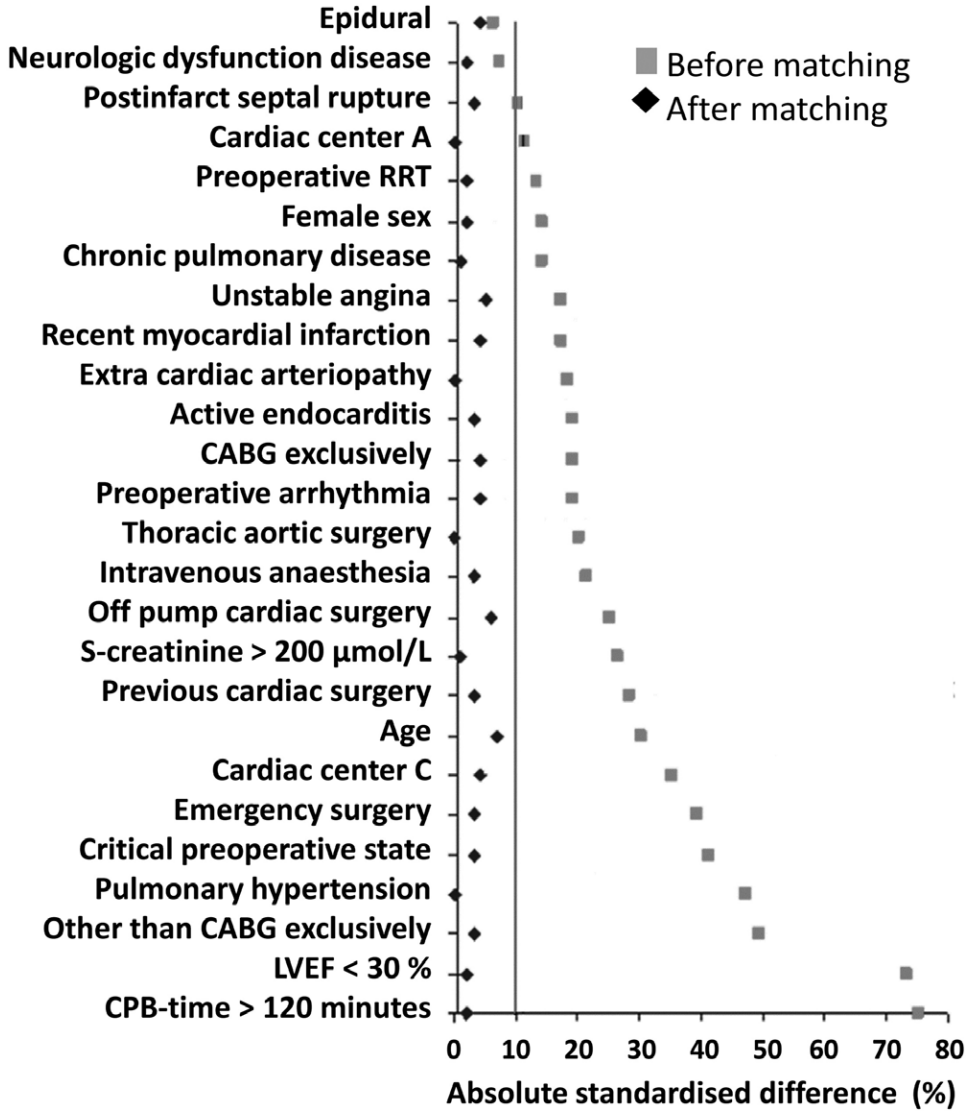


**Fig. 2.** Graphical representation of absolute standardized differences before and after propensity score matching comparing covariate values. *Solid fixed vertical line* represents the fixed limit of 10% for absolute standardized difference. CABG = coronary artery bypass grafting; CPB = cardio pulmonary bypass; LVEF = left ventricular ejection fraction; RRT = renal replacement therapy.

to statistical criteria as it has been shown that there was no association between the areas under the receiver operating characteristics curve (c-statistic) or any goodness-of-fit test and the ability of a given propensity score to accurately balance prognostically important variables between receivers and nonreceivers in a propensity score–matched sample.[18]

The matching was followed by a Cox regression analysis stratified for matched pairs in the analyses on mortality and conditional logistic regression of morbidity outcomes. In the regression analyses, we adjusted for provider characteristics, that is, the experience of the individual anesthesiologist and surgeon responsible for the intraoperative care. Two hundred twenty patients were initially excluded from study cohort due to missing data on either surgical procedure (33 patients), CPB time (57 patients), or inotrope treatment (130 patients). In the unmatched cohort, data were missing on 0.1 to 1.6% of predicting covariates. In the matched cohort information on all covariates were available for all patients except for information about attending surgeon in 14 patients, which were excluded in the following regression analysis. In the matched cohort, information was available for all patients on death and time of death. Seven patients had missing data on postoperative RRT, 12 patients on postoperative MI, 4 patients on stroke, and 14 patients on postoperative arrhythmia.

All data analyses were performed using Stata® 12.0 package (StataCorp LP, College Station, TX).

## Results

### Baseline Characteristics

The median age (interquartile range) of the 6,005 patients in the study was 68 yr (59 to 74); 8.8% of the patients were

older than 80 yr and 73% of the patients were men. The CABG procedure was performed in 66% of the patients. The overall rate of inotrope use either intraoperatively and/or postoperatively was 35% for the entire cohort. Patients receiving inotropes were older, had more comorbidities and worse cardiac conditions compared with nonreceivers. These patients were also more likely to have undergone more complex procedures such as valve surgery or combinations and had longer bypass time. Table 1 shows baseline characteristics for the entire study cohort as well for the propensity score–matched cohort (n = 2,340) according to inotropic use.

### Propensity Score–matched Cohort

Covariates associated with the use of inotropes and included in the propensity score matching are shown in table 1. In the matched cohort, the absolute standardized differences of all covariates were reduced to values below 10%, indicating that an adequate balance was achieved between treatment groups (fig. 2)

### Distribution of Perioperative Inotropes

Among 1,170 patients receiving inotropes in the matched cohort, 330 (28%) received a single-drug regime (dopamine

**Table 1.** Patient Characteristics of Cohort

| | Original Cohort | | | Propensity-matched Cohort | | |
|---|---|---|---|---|---|---|
| | No Inotrope Therapy | Inotrope Therapy | | No Inotrope Therapy | Inotrope Therapy | |
| | 3,908 | 2,097 | *P* Value | 1,170 | 1,170 | *P* Value |
| Demographics | | | | | | |
| Age (yr) | 66 (58–73) | 70 (62–76) | <0.0001 | 70 (62–76) | 70 (62–76) | 0.180* |
| Females | 977 (25.0) | 654 (31.2) | <0.0001 | 362 (30.9) | 354 (30.2) | 0.754† |
| EuroSCORE | 4.0 (2–7) | 8.0 (6–10) | <0.0001 | 6 (4–8) | 6 (4–8) | 0.751* |
| Patient-related EuroSCORE variables | | | | | | |
| Chronic pulmonary disease | 357 (9.1) | 285 (13.6) | <0.0001 | 123 (10.5) | 126 (10.8) | 0.893† |
| Extracardiac arteriopathy | 347 (8.9) | 308 (14.7) | <0.0001 | 124 (10.6) | 125 (10.7) | 1.0† |
| Neurologic dysfunction disease | 252 (6.4) | 169 (8.1) | 0.0234 | 74 (6.3) | 80 (6.8) | 0.677† |
| Previous cardiac surgery | 131 (3.4) | 32 (1.5) | <0.0001 | 62 (5.3) | 70 (6.0) | 0.531† |
| Serum creatinine >200 μmol/l | 56 (1.4) | 138 (6.6) | <0.0001 | 39 (3.3) | 37 (3.2) | 0.907† |
| Active endocarditis | 50 (1.3) | 93 (4.4) | <0.0001 | 32 (2.7) | 37 (3.2) | 0.625† |
| Critical preoperative state | 80 (2.0) | 267 (12.7) | <0.0001 | 47 (4.0) | 55 (4.7) | 0.479† |
| EuroSCORE—patient factors | *0 (0–1)* | *0 (0–3)* | <0.0001 | 0 (0–2) | 0 (0–2) | 1.0* |
| Other patient-related variables | | | | | | |
| Preoperative arrhythmia | 311 (8.0) | 441 (21.0) | <0.0001 | 168 (14.4) | 167 (14.3) | 1.0† |
| Preoperative RRT | 17 (0.4) | 39 (1.9) | <0.0001 | 13 (1.1) | 15 (1.3) | 0.900† |
| Cardiac-related EuroSCORE variables | | | | | | |
| Unstable angina | 297 (7.6) | 267 (12.7) | <0.0001 | 97 (8.3) | 114 (9.7) | 0.248† |
| Recent myocardial infarction | 716 (18.3) | 534 (25.5) | <0.0001 | 252 (21.5) | 235 (20.1) | 0.415† |
| Pulmonary hypertension | 104 (2.7) | 337 (16.1) | <0.0001 | 78 (6.7) | 77 (6.6) | 1.0† |
| LVEF ≤30% | 66 (1.7) | 399 (19.0) | <0.0001 | 60 (5.1) | 71 (6.1) | 0.369† |
| EuroSCORE—cardiac factors | 0 (0–0) | 0 (0–2) | <0.0001 | 1 (0–2) | 1 (0–2) | 0.930* |
| Procedure-related EuroSCORE variables | | | | | | |
| Emergency surgery | 157 (4.0) | 326 (15.5) | <0.0001 | 78 (6.7) | 88 (7.5) | 0.469† |
| CABG only | 2,687 (68.8) | 1,247 (59.5) | <0.0001 | 544 (44.7) | 524 (42.3) | 0.430† |
| Thoracic aortic surgery | 198 (5.1) | 195 (9.3) | <0.0001 | 82 (7.0) | 83 (7.1) | 1.0† |
| Postinfarct septal rupture | 6 (0.2) | 18 (0.9) | 0.0001 | 3 (0.3) | 5 (0.4) | 0.723† |
| EuroSCORE—procedure factors | 0 (0–2) | 2 (0–2) | <0.0001 | 2 (0–2) | 2 (0–2) | 0.326* |
| Other procedure-related variables | | | | | | |
| Intravenous anesthesia | 2,052 (52.5) | 877 (41.8) | <0.0001 | 501 (42.8) | 522 (44.6) | 0.405† |
| Epidural supplement | 375 (9.6) | 237 (11.3) | 0.0415 | 160 (13.7) | 144 (12.3) | 0.356† |
| CPB time >120 min | 654 (16.7) | 1,049 (50.0) | <0.0001 | 426 (36.4) | 415 (35.4) | 0.678† |
| Off-pump surgery | 581 (14.9) | 148 (7.1) | <0.0001 | 121 (10.3) | 102 (8.7) | 0.180† |
| Cardiac centre | | | | | | |
| Center A | 1,060 (27.1) | 466 (22.2) | | 284 (24.3) | 285 (24.4) | 0.616† |
| Center B | 1,995 (51.0) | 846 (40.3) | <0.0001 | 484 (41.4) | 504 (43.1) | |
| Center C | 853 (21.8) | 785 (37.4) | | 402 (34.4) | 381 (32.6) | |

Categorical data are numbers (%) and longitudinal data median (interquartile range).

* Mann–Whitney test. † Chi-square test.

CABG = coronary artery bypass grafting; CBP = cardiopulmonary bypass; LVEF = left ventricular ejection fraction; RRT = renal replacement therapy.

4%, epinephrine 1%, dobutamine 7%, and milrinone 17%); the remaining patients received a combination of two or more or a sequential treatment with different drugs.

### Distribution of Providers

Table 2 shows use of inotropic therapy according to provider experience based on number of cases per year for both attending anesthesiologists and surgeons. The seniority of attending anesthesiologists based on case numbers did not affect the use of inotropes in the matched cohort. Regarding surgeons, there was a significant difference in relation to experience between groups and use of inotropes. The medium volume group differed significantly from both high- and low-volume groups as fewer patients received inotropic treatment.

### Primary Outcomes

Among the propensity score–matched cohort, patients treated with inotropes had a cumulative 1-yr mortality of 11.1% (95% CI, 9.4 to 13.0) *versus* 4.2% (95% CI, 3.2 to 5.5) among nonreceivers (table 3). After adjusting for additional potential confounding dependent on provider, overall perioperative use of inotropic therapy was independently associated with an increased 1-yr mortality with an adjusted hazard ratio of 2.5 (95% CI, 1.8 to 3.5) (table 4). Figure 3 shows the cumulative 1-yr mortality risk by treatment status.

**Table 2.** Provider Distribution According to Use of Inotropic Therapy in Propensity-matched Cohort

| Provider | High Number | Medium Number | Low Number |
|---|---|---|---|
| Anesthetist* | | | |
| No inotrope | 456 | 255 | 459 |
| Inotrope | 440 | 249 | 481 |
| Surgeon† | | | |
| No inotropes | 390 | 310 | 465 |
| Inotropes | 442 | 242 | 477 |

Statistics: anesthetist, $P = 0.6466$; surgeon, $P = 0.0028$ (chi-square test).

* Divided in three groups based on at least one third of total cases in high and moderate group: High: > 40 cases per year; medium 16–40 cases per year; low: ≤15 cases per year. † Divided in three groups based on at least one third of total cases in high and moderate group: High: > 65 cases per year; medium 46 to 65 cases per year; low: ≤45 cases per year (missing data on 14 surgeons).

The curves did not overlap during follow-up and separated rapidly (fig. 3). Whether the timing of inotropic treatment was differently associated with mortality, inotropic treatment was divided into intraoperative treatment, postoperative treatment, or both (perioperative). For 1-yr mortality, intraoperative use was statistically significantly lower than postoperative and perioperative use ($P = 0.0380$; chi-square test). Figure 4 displays cumulative mortality risk stratified by timing of inotropic therapy.

### Secondary Outcomes

Use of inotropic therapy was independently associated with increased 30-day mortality (odds ratio [OR], 3.7; 95% CI, 2.11 to 6.53) (table 3). No difference was found between intraoperative, postoperative, and perioperative use and 30-day mortality ($P = 0.0940$; chi-square test) (fig. 4). Similarly, receivers of inotropic therapy had an adjusted increased risk of MI (OR, 2.1; 95% CI, 1.4 to 3.0), stroke (OR, 2.4; 95% CI, 1.4 to 4.3), and RRT (OR, 7.9; 95% CI, 3.8 to 16.4). However, perioperative inotrope treatment was not associated with postoperative arrhythmia (OR, 1.2; 95% CI, 1.0 to 1.4) (table 4). Finally, excluding off-pump patients from the analyses did not change risk estimates in all analyses (data not shown).

However, outcomes of excluded patients with missing data did not differ dramatically from outcomes in the study cohort. Thirty-day and 1-yr mortality was 4.1 and 10.9%, respectively, *versus* 3.2 and 7.6% in the unmatched study cohort. Excluded patients had higher logistic EuroSCORE 12.4 *versus* 8.9 in unmatched cohort, and would more likely have been allocated in treatment group, adding to a higher mortality.

## Discussion

In this population-based observational propensity score–matched study among cardiac surgery patients, we found a higher risk of adverse clinical outcomes in patients receiving inotropic therapy intra- and/or postoperatively compared with nonreceivers. The overall risk of postoperative mortality and morbidity in this study was in accordance with that in other similar studies.[19–21]

To our knowledge, the current study is, to date, the largest observational study on the association of perioperative

**Table 3.** Cumulative Incidence Risk and Hazard Ratios for Death by Treatment Status among Matched Cohort

| Endpoint | Number of Events | Number at Period Start | Cumulative Incidence Risk, % (95% CI) | HR (95% CI) | Adjusted HR* (95% CI) |
|---|---|---|---|---|---|
| 30-day mortality | | | | | |
| No inotropes | 16 | 1,170 | 1.37 (0.84–2.22) | 1 (reference) | 1 (reference) |
| Inotrope treatment | 59 | 1,170 | 5.06 (3.94–6.48) | 3.69 (2.12–6.41) | 3.71 (2.11–6.53) |
| One-year mortality | | | | | |
| No inotropes | 49 | 1,170 | 4.19 (3.18–5.50) | 1 (reference) | 1 (reference) |
| Inotrope treatment | 129 | 1,170 | 11.06 (9.39–13.01) | 2.51 (1.80–3.50) | 2.49 (1.78–3.48) |

* Adjusted by anesthetist and surgeon provider group (table 2).

HR = hazard ratio.

**Table 4.** Odds Ratios of In-hospital Complications by Treatment Status among Matched Cohort

| In-hospital Complications | Number of Events | OR (95% CI) | Adjusted OR* (95% CI) |
|---|---|---|---|
| RRT | | | |
| No inotropes | 13 | 1 (reference) | 1 (reference) |
| Inotrope treatment | 79 | 7.0 (3.72–13.17) | 7.89 (3.80–16.42) |
| MI | | | |
| No inotropes | 45 | 1 (reference) | 1 (reference) |
| Inotrope treatment | 88 | 2.02 (1.40–2.93) | 2.06 (1.41–3.02) |
| Stroke | | | |
| No inotropes | 19 | 1 (reference) | 1 (reference) |
| Inotrope treatment | 47 | 2.61 (1.52–4.50) | 2.42 (1.37–4.28) |
| Arrhythmia | | | |
| No inotropes | 387 | 1 (reference) | 1 (reference) |
| Inotrope treatment | 428 | 1.17 (0.98–1.38) | 1.15 (0.97–1.37) |

* Adjusted by anesthetist and surgeon provider group (from table 2).
MI = myocardial infarction; OR = odds ratio; RRT = renal replacement therapy.

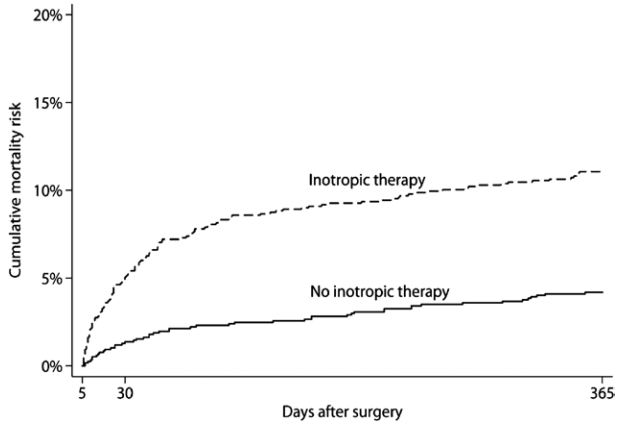


**Fig. 3.** Cumulative 1-yr mortality risk by treatment status. Log-rank *P* value <0.00001.

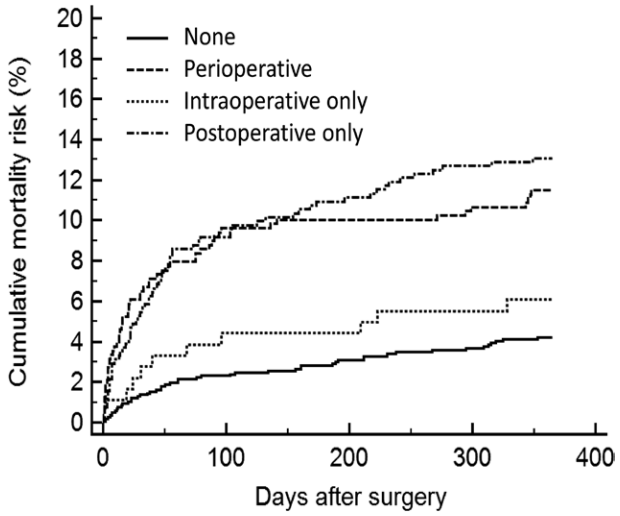


**Fig. 4.** Cumultative 1-yr mortality risk stratified by timing of inotropic therapy. Log-rank *P* value <0.0001.

inotrope use in cardiac surgery and mortality and morbidity. The study has several strengths. The extensive preoperative, intraoperative, and postoperative data were prospectively collected in a large population of patients undergoing cardiac surgery. The large amount of data collected made it possible to control for many potential confounders. Patients were recruited from three cardiac centers, and propensity matching on center-affiliation minimized possible single-center bias. Furthermore, experience of providers was incorporated in the analysis to avoid bias and we had complete follow-up on major outcome parameters.

Results should be interpreted with caution as observational studies always carry a risk of residual confounding. Propensity matching on basic patient characteristics such as preoperative comorbidity, cardiac condition including preoperative left ventricular function, and type of procedure allowed us to control for major patient-related confounders. However, we were not able to include neither intraoperative hemodynamic parameters nor intraoperative echocardiography evaluations at initiation of inotropic therapy; residual confounding may exist relating to intraoperative events either due to worse preexisting cardiac disease than measured by preoperative left ventricular function or relating to intraoperative factors such as reperfusion injury or cardioplegia-induced myocardial dysfunction not necessarily accounted for by procedure scoring.

None of the study centers used goal-directed therapy and it could be discussed whether inotropes were used optimally and started and stopped appropriately. This may have negatively affected the risk of adverse outcomes. The power of the current cohort size, however, may have minimized this potential bias.

Missing data could be a source of uncontrolled bias. However, due to the low range of missing data in our data, it is unlikely to influence the results significantly. It is also important to note that patients who only received vasopressor therapy were completely excluded from the analysis. This is a unique population that may actually do better than patients represented in the current article. Despite these limitations, we believe the results show an underlying signal regarding the potentially harmful effect of perioperative

inotropic therapy. Our results support the findings of two other important observational studies. Fellahi *et al*. reported that catecholamine administration was associated with major cardiac morbidity. In an initial cohort of 667 patients, perioperative use of catecholamines was associated with increased cardiac morbidity measured as a combined endpoint of postoperative sustained ventricular arrhythmia, need for an intraaortic balloon pump in ICU or postoperative MI. The magnitude of harmful effects ranged from OR of 1.8 to 3.0 depending on analytical strategy. However, in a propensity score–matched subgroup analysis of 162 patients, the authors could not identify a significant association with in-hospital mortality, probably due to lack of sample size power.[3] Fellahi *et al.* did not report any association with RRT. In another study of 1,326 cardiac surgery patients, Shahin *et al*. found postoperative inotrope use to be independently associated with increased in-hospital mortality (OR, 2.3; 95% CI, 1.2 to 4.5) and renal dysfunction OR (2.7; 95% CI, 1.5 to 4.6) by using multivariate analysis. Using propensity score matching on 246 patients of the original cohort, they found that mortality was increased 10-fold in patients receiving inotropic therapy and renal dysfunction was increased six-fold compared with nonreceivers of inotropic therapy. An association with MI and postoperative arrhythmia was not reported.[5]

The current study adds important knowledge to existing studies. The large study sample allowed us to estimate the association between use of inotropes and a range of individual rather than combined adverse endpoints including short- and long-term mortality. The magnitude of the associations between inotropic therapy and adverse outcomes in our study were within the range of risk estimates reported by Fellahi *et al.*[3] and Shahin *et al*.[5]

Recent updates and meta-analyses on inotropic agents in the perioperative setting in cardiac surgery have failed to identify placebo-controlled trials sufficiently powered to detect clinically meaningful differences on mortality and major postoperative morbidity.[2,22,23] In studies of nonsurgical heart failure, several observational as well as placebo-controlled studies of inotropes in acute or chronic heart failure have shown poorer clinical outcomes in patients receiving inotropes.[24–27] These data from studies of inotropes used in cardiac failure in nonsurgical situations support our findings of an increased risk for adverse outcomes when inotropes are used perioperatively.

The current study does not clearly address the question concerning the time during the perioperative process where inotropes may be most harmful. Separate analyses dividing the patients into three types of therapy (1) none, (2) intraoperative with or without postoperative therapy, and (3) postoperative therapy revealed that patients receiving only intraoperative therapy had the lowest 1-yr mortality compared with two other groups in the propensity-matched cohort. These results may indicate that inotropic therapy exclusively used for coming off CPB may be safer than prolonged or delayed postoperative use of inotropes. However, interpretation of these results is warranted, as the current study was not designed to address this question.

Several mechanisms may explain the observed increase in mortality rate among patients exposed to inotropes. Both phoshodiesterase inhibitors and dobutamine carry a significant risk of atrial and ventricular arrhythmias, presumably related to increases in intracellular calcium levels.[25,28] Patients with new arrhythmias during an exacerbation of heart failure constitute a high-risk group with higher in-hospital and 60-day morbidity and mortality.[29] However, the current study could not show an increased risk of postoperative arrhythmias related to use of inotropes and alternative explanations should thus be considered.

Increased contractility and temporary improvement in cardiac performance may be at the expense of increasing myocardial energy consumption and acceleration of myocardial cell death. It has been suggested that increase in contractility of the hibernating myocardium by low doses of inotropes can lead to a perfusion–contraction mismatch with an activation of anaerobe glycolysis and eventually myocardial necrosis.[30,31] Thus, despite the apparent clinical improvement, there may be a risk of progression of heart failure in patients exposed to inotropes.

Despite accumulating evidence of possible long-term harmful effects of inotropes, intravenous inotropes are recommended in patients with advanced acute decompensated heart failure as seen in low cardiac output syndrome after cardiac surgery.[32] Recent guidelines on the management of acute and perioperative heart failure have suggested algorithms for pharmacological treatment of low cardiac output syndrome, but emphasized that the optimal use of inotropes remains controversial.[33] In a recent published benefit/risk analysis by Fellahi *et al.*,[34] it was emphasized that current inotropic drugs have failed to show beneficial effects beyond short-term hemodynamic improvement in acute heart failure and attention is drawn to development of new agents that may increase benefits and decrease risks of current inotrope agents.

Our data support, except when given intraoperatively only, that inotrope use is potentially harmful. However, the concept that inotropes carry real risks must be weighed against potential benefits on a per-patient basis. For example, in patients with baseline left ventricular ejection fraction less than 30%, use of inotropic therapy may be the only option for the anesthesiologists at the end of CPB. Thus, further studies on the safety and efficacy on clinical outcome parameters of different inotrope treatments are warranted.

## Conclusion

We demonstrated that perioperative use of inotropes was associated with increased mortality and postoperative morbidity among cardiac surgery patients. These findings add to the knowledge base from previous smaller studies. However,

the findings stress the need for an improved body of evidence to guide the clinical practice of inotropic therapy.

## Acknowledgments

The authors thank all surgeons and anesthesiologists who have participated in the registration of patients in the Western Danish Heart Registry at the following institutions: Department of Anesthesiology and Intensive Care, Aarhus University Hospital, Aarhus, Denmark; Department of Anesthesia and Intensive Care, Odense University Hospital, Odense, Denmark; and Department of Anesthesia and Intensive Care, Aalborg University Hospital, Aalborg, Denmark.

The study was funded by an unrestricted research grant (No. 10-04-R78-A2905-22611) from The Danish Heart Foundation, Copenhagen, Denmark, and from the Research Council of the Central Denmark Region, Viborg, Denmark.

## Competing Interests

The authors declare no competing interests.

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