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# Continuous postoperative pericardial flushing reduces postoperative bleeding after coronary artery bypass grafting: A randomized trial

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ABSTRACT

*Background:* Prolonged or excessive bleeding after cardiac surgery can lead to a broad spectrum of secondary complications. One of the underlying causes is incomplete wound drainage, with subsequent accumulation of blood and clots in the pericardium. We developed the continuous postoperative pericardial flushing (CPPF) therapy to improve wound drainage and reduce postoperative blood loss and bleeding-related complications after cardiac surgery. This study compared CPPF to standard care in patients after coronary artery bypass grafting (CABG).

*Methods:* This is a single center, open label, randomized trial that enrolled patients at the Amsterdam UMC, location AMC, Amsterdam, the Netherlands. The study was registered at the 'Netherlands Trial Register', study identifier NTR5200 [1]. Adults undergoing CABG were randomly assigned to receive CPPF therapy or standard care, participants and investigators were not masked to group assignment. The primary end point was postoperative blood loss in the first 12-hours after surgery.

*Findings:* Between the January 15, 2014 and the March 13, 2017, 169 patients were enrolled and assigned to CPPF therapy (study group; $n$ = 83) or standard care (control group; $n$ = 86). CPPF reduced postoperative blood loss when compared to standard care (median differences -385 ml, reduction 76% $p$=≤0.001), with the remark that these results are overestimated due to a measurement error in part of the study group. None of patients in the study group required reoperation for non-surgical bleeding versus 3 (4%, 95% CI -0.4% to 7.0%) in the control group. None of the patients in the study group suffered from cardiac tamponade, versus 3 (4%, 95% CI -0,4% to 7.0%) in the control group. The incremental cost-effectiveness ratio was €116.513 (95% bootstrap CI €-882.068 to €+897.278).

*Interpretation:* The use of CPPF therapy after CABG seems to reduce bleeding and bleeding related complications. With comparable costs and no improvement in Qualty of Life (QoL), cost consideration for the implementation of CPPF is not relevant. None of the patients in the study group required re-interventions for non-surgical bleeding or acute cardiac tamponade, which underlines the proof of concept of this novel therapy.

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## 1. Introduction

Prolonged or excessive bleeding is a common complication after cardiac surgery that may trigger a broad spectrum of secondary bleeding-related complications and is associated with increased

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**Research in context**

*Evidence before this study*

In 2015, our group was the first to demonstrate the safety and feasibility of Continuous Postoperative Pericardial Flushing (CPPF) in a pilot study. In a recently published randomized controlled trial, we investigated the efficacy of CPPF compared to standard care in a heterogeneous group of cardiac surgery patients. We found a blood loss reduction 12 h after arrival in the ICU of 155 ml (41%) in the CPPF group when compared to standard care.

*Added value of this study*

In the present trial we investigated the efficacy of CPPF in a more homogenous group of cardiac surgery patients undergoing coronary artery bypass grafting (CABG). In this group we aimed for a more distinctive treatment effect in a group of patients that tend to bleed more due to the use of anti-platelet therapy. When calculated as prescribed in the study protocol, CPPF significantly reduced postoperative blood loss after 12-hour stay in the ICU (−76%) when compared to standard care (median differences −385 ml, $p$=≤0.001). None of the patients in the study group required reoperation for non-surgical bleeding versus 3 (4%, CI −0.4% to 7.0%) in the control group and acute cardiac tamponade did not occur in any of the patients in the study group, versus 3 (4% CI −0.4% to 7.0%) in the control group..

*Implications of all the available evidence*

Comparable findings were obtained by Kara and Erden, who used a similar CPPF protocol to evaluate the safety and feasibility in a group of 42 patients that underwent isolated CABG. They observed no method related complications and a reduction in mean blood loss of 257.24 ml (38%) in the CPPF group. Pooled data of our two randomized trials, both concerning cardiac surgery patients, showed significant differences for clinically important secondary end-points like re-interventions for non-surgical bleeding or acute cardiac tamponade (CPPF groups 0 versus 8 in the standard care group, $p$ = 0.007). The freedom of incidents in the CPPF groups underline the proof of concept that CPPF is able to minimize or even eliminate these sometimes life-threatening complications after cardiac surgery.

morbidity and mortality [2, 3]. Prolonged or excessive bleeding is associated with longer intensive care unit (ICU) and hospital stay, more (re)admissions to the ICU and are therefore associated with higher hospitalization costs [4].

Standard postoperative care comprises chest drainage with tubes connected to a low-pressure suction system to evacuate blood and clots from the pericardial and mediastinal spaces and to monitor bleeding rate. However, chest tubes may become obstructed by clots and consequently fail, leading to stasis of blood and clots in the pericardial cavity. (video 1, see online appendix) [3] It has been demonstrated that this retained blood and clots lead to even more fibrinolytic activity in the mediastinum and pericardial space, and therefore may contribute to increased or prolonged bleeding [5, 6]. This hypothesis is also supported by the frequently observed clinical finding that during re-exploration for postoperative bleeding, removal of accumulated blood and clots by solely irrigating the pericardial space with a warm saline solution alone is often sufficient to stop the bleeding immediately. Based on this principle, the method of continuous postoperative pericardial flushing (CPPF) was developed at our institution. Continuous postoperative flushing aims to prevent the formation of larger clots, thereby preventing chest tube blockage, which facilitates the evacuation of blood. (video 2, see online appendix)

Results from our previous randomized controlled trial (RCT) showed a postoperative blood loss reduction of 41% [7]. The study population of this previous study had a relatively low risk and were younger-aged congenital patients with few comorbidities compared to the CABG population. Generally, blood loss is more in the CABG population due to the use of antiplatelet medication and a larger internal wound due to internal mammary artery harvesting, therefore anticipating a more pronounced effect of CPPF. In the current study we evaluated the effects of CPPF versus standard care on postoperative blood loss, related complications, costs and QoL after surgery in patients undergoing elective CABG.

## 2. Methods / design

### 2.1. Design and objectives of the trial

We conducted a single center, open label, randomized 2-arm trial at the Amsterdam University Medical Center (Amsterdam UMC), location AMC, Amsterdam, the Netherlands. The study was conducted in accordance with the declaration of Helsinki and was registered on June 14, 2015 at the 'Netherlands Trial Register', study identifier NTR5200 and at the Centrale Commissie Mensgebonden Onderzoek (CCMO; www.ccmo.nl) reference NL43190.018.13. The study was supported by a grant from 'Zorgonderzoek Medische Wetenschappen' (ZonMw), the Dutch organization for health research and development and intramural resources of the Amsterdam UMC, location AMC. Investigators affiliated with the Heart Center at the Amsterdam UMC, location AMC, designed the study, collected and managed data and performed statistical analysis. The study protocol, available in the online appendix, was approved by the Institution Ethical Review Board of the Amsterdam UMC, location AMC, reference METC2013_006. This study had an events adjudication committee, and a data and safety monitoring board overseeing the study. The Amsterdam UMC held the clinical database and the coordinating investigator had unrestricted access to the data.

### 2.2. Participants

We enrolled patients scheduled for elective CABG. Exclusion criteria included: previous CABG, emergency surgery and preoperative use of one of the following oral anticoagulants (Dabigatran, Rivaroxaban, Apixaban, Clopidogrel, Brilique or Prasugrel). Full inclusion and exclusion criteria are summarized in the online appendix. Patients meeting all inclusion criteria and no exclusion criteria were invited to participate in the study and gave written informed consent one day prior to surgery. Participants and investigators were not masked for treatment allocation.

In an amendment to the Medical Ethics Committee (MEC) on December 2016 the trial steering committee requested and obtained permission to include 10 additional patients to compensate a higher drop-out than expected and thereby ensure 170 evaluable patients at the end of the study. Consequently, the number of patients needed for inclusion was increased from 170 to 180 patients. The study is reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (see online appendix).

### 2.3. Procedures

Patients were randomly assigned by the coordinating investigator, in a 1:1 ratio, to receive either CPPF therapy (study group) or standard care (control group). Randomization was performed on site in the operating theatre immediately after surgical haemostasis was

achieved and prior to routine insertion of the chest tubes and subsequent sternal closure. We used ALEA web-based randomization software (block size range 6 to 12). Patients randomized to the control group had one chest tube inserted into the pericardial space, one in the anterior mediastinum, and one in each surgically-opened pleural cavity. In patients randomized to the study group, an additional infusion tube was inserted through a separate small incision between the chest tube incisions and positioned in the pericardial space. This extra infusion tube was directly connected to the CPPF system. The CPPF system connects an infusion line that runs through a volumetric pump and through a fluid heating device to deliver the irrigation solution at a constant temperature of approximately 310 Kelvin and at a fixed flow rate of 500 ml/hour until the total irrigation volume of 7000 ml had been infused. CPPF started immediately after sternal closure.

Red cell transfusion was considered when hemoglobin level $<$5.0 mmol/l, platelet concentrate transfusion when platelet count $<50 \times 109$/l or $<100 \times 109$/l if postoperative blood loss exceeded 150 ml/hour, and fresh frozen plasma administration was considered when activated partial thromboplastin time and prothrombin time $>$150% during active bleeding in accordance with local ICU protocol. Triggers for surgical re-exploration were based on postoperative blood loss volumes which were approximately $>$500 ml/hour, $>$400 ml/hour during the first two hours, $>$300 ml/hour/3hours, $>$200 ml/hour/$\geq$4hours, and $>$1000 ml in total with normal coagulation parameters. Standard ICU protocol for chest tube removal was respected in both groups and all inserted tubes were removed simultaneously.

### 2.4. Follow up and end points

The primary end point was postoperative blood loss after a 12-hour stay in ICU. For those patients who received standard care, postoperative blood loss was defined as the total mediastinal chest tube drainage (MCTD) volume originating from the combined pericardial, mediastinal, and pleural cavities. For the patients who received care with the CPPF therapy, postoperative blood loss was calculated by subtracting the total CPPF irrigation volume from the total MCTD volume. When the total irrigation fluid volume exceeded the total MCTD volume it resulted in virtual “negative postoperative blood loss”. As observed in our previous study, sometimes part of the irrigation fluid seems to accumulate in the pericardial or pleural space(s) and/or was absorbed by the epithelial surface in these body cavities. [7] Although negative blood loss is not possible, no corrections were made for patients with negative postoperative blood loss. Secondary analyses included were on per protocol basis and sensitivity analyses exploring the influence of the three surgically opened pleural cavity subgroups.

Secondary outcomes included total postoperative blood loss, delta haemoglobin (between randomization and a 12-hour stay in ICU and between randomization and hospital discharge), blood transfusions between randomization and hospital discharge, time between randomization and arrival at ICU, duration of chest tube drainage, fluid accumulation in the pericardial and/or pleural spaces at hospital discharge, and bleeding-related adverse events. Other secondary endpoints consisted of duration of mechanical ventilation, length of ICU stay and total hospitalization time.

Recorded bleeding-related adverse events included the occurrence of acute and late ($\leq$30 days after chest tube removal) cardiac tamponade, reoperation (e.g. for surgical bleeding, non-surgical bleeding, and other reason), intervention for pericardial or pleural effusion (e.g. subxyphoid pericardial drainage or pericardial puncture), infection (e.g. sepsis, pneumonia, superficial wound infection, deep sternal wound infection, and other infection), delirium, acute renal insufficiency, new onset postoperative atrial fibrillation, myocardial infarction, and all-cause mortality. Adverse events were recorded in accordance with the Center for Disease Control criteria for infection [8] and the Society of Thoracic Surgeons Adult Cardiac Surgery Database Data Specifications. [9] A masked local critical events committee adjudicated all bleeding-related adverse events. Imaging was interpreted by physicians unaware of treatment allocation.

Clinical follow-up information was obtained at the outpatient cardiac clinic of the study center or determined from information acquired from the patients referral hospital. All patients were seen by an attending cardiologist one month after discharge. Follow-up assessments included chest X-ray, immediately after surgery and after 5–7 days. Transthoracic echocardiography (TTE) was routinely conducted before discharge and 6 months after the surgery. We used the Dutch version of the EQ-5D to assess the QoL and the short-form health survey (SF-HLQ) to estimate productivity loss. [10,11] Use of healthcare resources were recorded prospectively by means of a modified SF-HLQ questionnaire at six-month follow-up and from the electronic patient files in the referral hospitals and study center. Healthcare unit costs were sourced from the procurement and finance department at the study center and if not provided by the procurement and finance department, unit costs were derived from national databases. Utility scores were calculated [7,10] based on data obtained by means of an EQ-5D-5 L at intake and at six-month follow-up.

To quantify the extra cost of obtaining an additional unit of outcome an incremental cost-effectiveness ratio (ICER) was calculated. The costs of medical care during treatment and follow-up were calculated, divided into direct medical cost (health care utilization inside and outside the hospital) and indirect cost (lost productivity due to absence from work). Costs are defined as the volumes of used resources multiplied by calculated unit prices.

### 2.5. Statistical analysis

The study was designed to test whether CPPF was superior to standard care, as determined by postoperative blood loss after 12-hour stay in the ICU. The study was powered to detect a difference of 213 ml postoperative blood loss after 12-hour stay in the ICU, based on a small pilot study [12], with a power of 95%, a two-sided alpha of 5%, and accommodated for $\approx$5% drop out. A total sample of 85 patients per group was required. The differences in baseline characteristics between both treatment groups were assessed without imputation for missing data. Categorical data are reported as numbers and percentages and the differences between groups were tested using Fisher’s exact tests. Continuous data with a normal distribution are summarized as means and standard deviation (SD) and analyzed using the unpaired *t*-test, whereas the non-normally distributed data are presented as medians with interquartile ranges (IQR) and analyzed using the Mann-Whitney U test. The primary analysis was performed according to the intention-to-treat principle according to a pre-specified statistical analysis plan (SAP, see online appendix) Since we did not want to make any distributional assumptions with respect to the postoperative blood loss after 12-hour stay in the ICU, we reported postoperative blood loss as medians with IQR. The difference between both groups was tested using the Mann-Whitney U test. Indirect costs were calculated in the base case analysis, using the friction cost method. The Dutch social tariff for the EQ-5D-5 L [10], completed at baseline and 6 months after surgery, was applied to calculate utility values. The incremental cost-effectiveness ratio (ICER) was calculated using mean estimates of costs and utility gain. One thousand bootstraps were generated for each sample for the probabilistic sensitivity analysis. For hypothesis tests, two-tailed P values $<$0.05 with confidence intervals are considered statistically significant. In an additional per protocol (PP) analysis, excluding all patients randomized but failed to receive their allocated treatment, we checked the robustness of the results. Sample size was calculated

CONSORT diagram showing the flow of participants through each stage of a randomized trial.

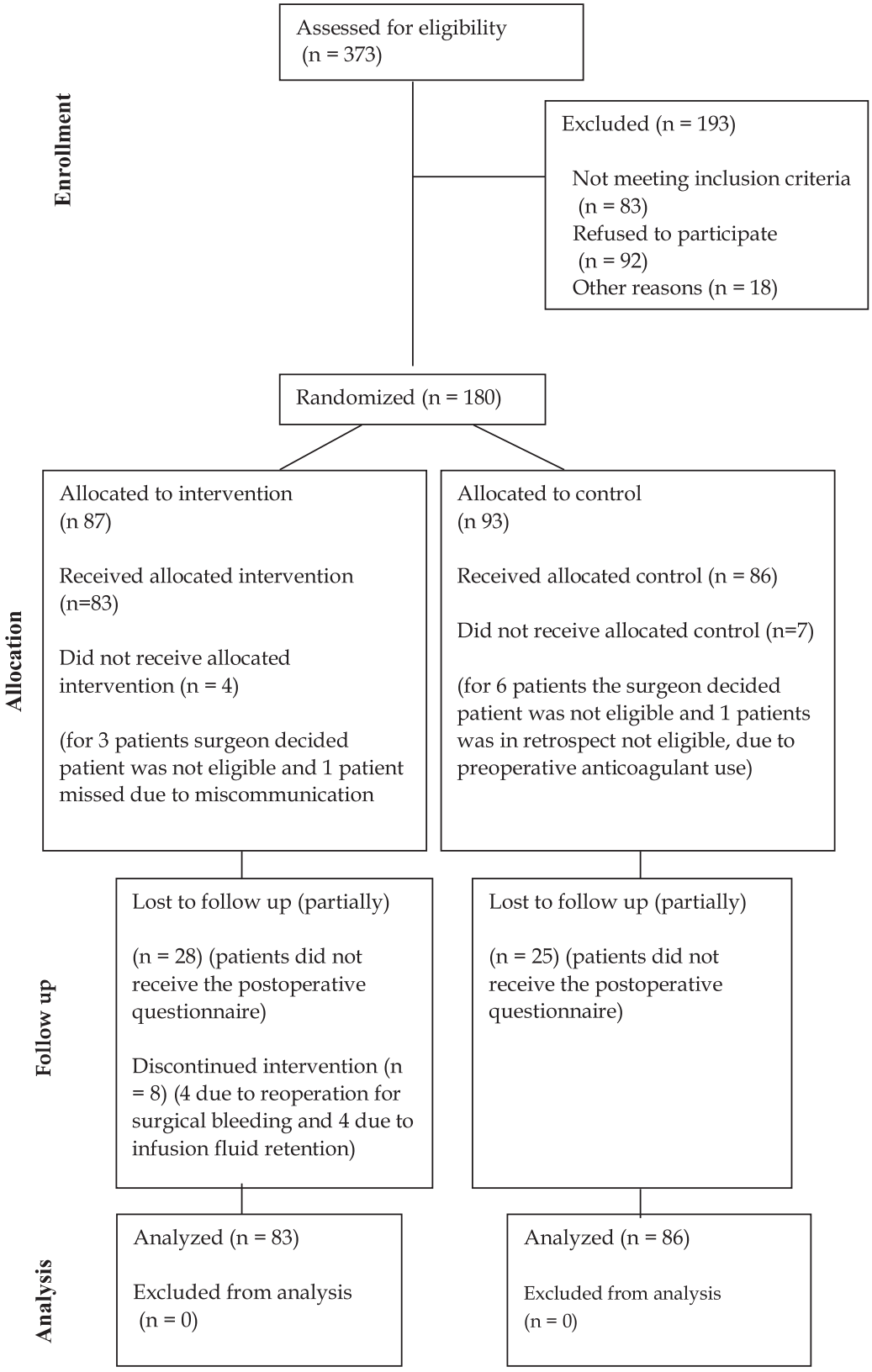


**Fig. 1.** CONSORT diagram showing the flow of participants through each stage of a randomized trial.

using N Query Advisor (version 7.0) software for Windows, study source data were stored in Oracle® Clinical Remote Data Capture (version 4.5.3) and Castor® cloud-based data solution, analyses were performed using IBM® SPSS® statistics (version 24.0) software for Windows and R base software for Windows.

### 2.6. Role of the funding source

This was an academic investigator-initiated study funded by ZonMw, the Netherlands organization for health research and development (project 837,001,405) and intramural resources of the Academic Medical Center, Amsterdam, the Netherlands. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## 3. Results

Between January 15, 2014 and the March 13, 2017, 373 patients were assessed for eligibility. Of these patients 193 were excluded (Fig. 1); 180 patients provided written informed consent and after randomization 11 patients were excluded. For three patients the surgeon decided intraoperatively, after randomisation, that the patient was not eligible to receive the allocated intervention. The six patients that were operated on by the same surgeon, but were allocated to the control group during this non-cooperative period were also excluded. One patient was excluded after randomization to the control group since in retrospect this patient was not eligible for inclusion due to preoperatively use of anticoagulant which is one of the exclusion criteria. One patient did not receive the allocated intervention due to miscommunication between the researcher and the operating room. Therefore, in an amendment to the MEC on December 2016 the trial steering committee requested and obtained permission to include 10 additional patients.as explained above. One more patient, randomization to the control group, was excluded since, in retrospect, this patient was not eligible for inclusion due to preoperatively use of anticoagulant which is one of the exclusion criteria, resulting in a CPPF group (study) of 83 patients and a standard care (control group) of 86 patients. Baseline clinical characteristics were balanced between groups (Table 1) [13, 14] Procedural characteristics were similar between groups, except for the use of intra-operative platelet concentrate which was slightly used more often in the control group ($p = 0.029$) (Table 2).

Infusion tube placement and start of treatment was successfully performed in all 83 patients allocated to the study group. Treatment was completed in 75 (90%) patients and discontinuation was needed in 8 (10%) patients in the study group. Four patients required emergency reoperation for surgical bleeding and four patients had accumulation of >200 ml infusion fluid, and treatment was discontinued according to the protocol.

The analysis of the primary outcome in the intention-to-treat population showed that median postoperative blood loss after 12-hour stay in the ICU was reduced with 76% in the study group when compared to the control group (120 ml, IQR −270 to 500 vs. 505 ml, IQR 350 to 753; $p<0.001$) (Table 3). The treatment effect was slightly larger in the per-protocol analysis ($p<0.001$) (Table 4).

Median total postoperative blood loss at chest tube removal was 475 ml (IQR 50 to 925) in the study group versus 725 ml (IQR 517 to 1052) in the control group ($p = 0.001$). At hospital discharge, patients in the study group were less likely to have pericardial effusion on their echocardiogram at discharge when compared to the control group (2% vs. 7%; $p = 0.182$) but this did not reach statistical significance. The reduction of 12-hour and total postoperative blood loss did not lead to significant differences in mean delta hemoglobin between randomization and 12-hour stay in the ICU (0.26 ± 0.62 vs.

**Table 1**
Baseline clinical characteristics*.

| | Study group ($n = 83$) | Control group ($n = 86$) | P |
|---|---|---|---|
| Age (years) | 69 (63 to 74) | 68 (61 to 74) | 0.547 |
| Sex (no. males) | 68 (82%) | 75 (87%) | 0.397 |
| Body-mass index † | 27 (25 to 30) | 27 (25 to 29) | 0.611 |
| Diagnoses and associated diseases: | | | |
| Chronic obstructive pulmonary disease | 8 (10%) | 11 (13%) | 0.628 |
| Renal insufficiency (at least moderate) | 49 (59%) | 40 (47%) | 0.124 |
| Renal insufficiency (severe) | 9 (11%) | 6 (7%) | 0.427 |
| Cerebrovascular accident of transient ischemic attack | 8 (10%) | 11 (13%) | 0.628 |
| NYHA class: ‡ | | | |
| I & II | 30 (37%) | 31 (37%) | 1.000 |
| III & IV | 51 (63%) | 54 (64%) | 1.000 |
| EuroSCORE II | 1.28 (0.78 to 2.16) | 1.33 (0.84 to 2.24) | 0.555 |
| Left ventricular ejection fraction: | | | |
| >50% | 59 (71%) | 64 (75%) | 0.603 |
| 30−50% | 23 (28%) | 19 (22%) | 0.478 |
| <30% | 1 (1%) | 2 (2%) | 1.000 |
| Hemoglobin (g/dL) | 8.7 (8.2 to 9.3) | 9.0 (8.3 to 9.5) | 0.160 |
| Preoperative anti-coagulants § | | | |
| None | 2 (2%) | 3 (4%) | 1.000 |
| Single | 63 (76%) | 56 (65%) | 0.133 |
| Double | 17 (21%) | 24 (28%) | 0.286 |
| Triple | 1 (1%) | 3 (4%) | 0.621 |

* Data before randomization. Data are presented as numbers (percentages) or median and InterQuartile Range (IQR), unless otherwise specified.
† Data on body-mass index (the weight in kilograms divided by the square of the height in meters).
‡ New York Heart Association (NYHA) classes range from I to IV.
§ Use of all antiplatelet agents was discontinued 5 days prior to surgery.

**Table 2**
Procedural data*.

| | Study group ($n = 83$) | Control group ($n = 86$) | P |
|---|---|---|---|
| **Number of surgical procedures** | | | |
| Single procedure | 63 (76%) | 60 (70%) | 0.392 |
| Double procedure | 15 (18%) | 19 (22%) | 0.568 |
| Triple procedure | 3 (3.6%) | 6 (7.0%) | 0.496 |
| Quadruple procedure | 2 (2%) | 1 (1%) | 0.616 |
| Procedures per patient median (IQR) | 1 (1 to 1) | 1 (1 to 2) | 1.000 |
| **Procedure type** | | | |
| Aortic root surgery | 0 (0%) | 1 (1.2%) | 1.000 |
| **Operative data** | | | |
| Off pump | 12 (15%) | 9 (11%) | 0.489 |
| Cardiopulmonary bypass duration (min) | 100 (88 to 125) | 100 (80 to 125) | 0.507 |
| Cross-clamp duration (min) | 66 (55 to 90) | 64 (49 to 89) | 0.319 |
| Operation duration (min) | 250 (210 to 304) | 239 (199 to 300) | 0.514 |
| Number of surgically opened pleural cavities: | | | |
| None | 13 (16%) | 15 (17%) | 0.837 |
| One | 45 (54%) | 52 (61%) | 0.440 |
| Two | 25 (30%) | 19 (22%) | 0.293 |
| Patients transfused before randomization: | | | |
| Red cells | 20 (24%) | 12 (14%) | 0.117 |
| Fresh-frozen plasma | 0 (0%) | 1 (1.2%) | 1.000 |
| Platelet concentrate | 0 (0%) | 6 (7.0%) | 0.029 |
| Fibrinogeen | 1 (1%) | 6 (7%) | 0.118 |
| Cell-saver blood | 68 (82%) | 68 (79%) | 0.700 |
| Cell-saver blood reinfused (ml) median (IQR) | 480 (444 to 623) | 483 (400 to 700) | 0.853 |

* Data before randomization. Data are presented as numbers and percentages or median and InterQuartile Range (IQR), unless otherwise specified.

**Table 3**
Primary and secondary outcomes *.

| | Study group ($n$ = 83) | | Control group ($n$ = 86) | | $P$ |
|---|---|---|---|---|---|
| | n/total n † | | n/total n† | | |
| **Primary outcome** | | | | | |
| Postoperative blood loss after 12-hour stay in the ICU | 83/83 | 120 (−270 to 500) | 86/86 | 505 (350 to 753) | <0.001 |
| **Secondary outcomes** | | | | | |
| Postoperative blood loss at chest tube removal | 83/83 | 475 (50 to 925) | 86/86 | 725 (517 to 1052) | < 0.001 |
| Hemoglobin Δ between randomization and 12-hour stay in the ICU (g/dL) | 81/83 | 0.30 (−0.10 to 0.65) | 86/86 | 0.30 (−0.20 to 0.70) | 0.971 |
| Hemoglobin Δ between randomization and hospital discharge (g/dL) | 81/83 | −0.60 (−1.10 to 0.20) | 85/86 | −0.30 (−1.10 to 0.20) | 0.406 |
| Patients transfused after randomization: | | | | | |
| Red cells | 82/83 | 27 (33%) | 84/86 | 23 (27%) | 0.500 |
| Fresh frozen plasma | 83/83 | 1 (1%) | 86/86 | 3 (4%) | 0.621 |
| Platelet concentrate | 83/83 | 3 (4%) | 86/86 | 10 (12%) | 0.081 |
| Fluid accumulation at discharge | | | | | |
| Pericardial effusion on echocardiogram (≥10 mm) | 62/83 | 1 (2%) | 54/86 | 4 (7%) | 0.182 |
| Pleural effusion on chest X-ray | 83/83 | 59 (87%) | 86/86 | 67 (85%) | 0.816 |
| in a surgically opened pleural cavity | 69/83 | 47 (68%) | 79/86 | 54 (68%) | 1.000 |
| **Time-related data** | | | | | |
| LOS ICU, hours | 83/83 | 23 (20 to 48) | 86/86 | 25 (20 to 44) | 0.756 |
| LOS hospital, days | 78/83 | 8 (7 to 10) | 75/86 | 8 (7 to 10) | 0.333 |
| Time until chest tube removal, hours | 47/83 | 45 (40 to 50) | 42/86 | 43 (31 to 51) | 0.477 |
| Time until detubation, hours | 83/83 | 7 (4 to 10) | 86/86 | 6 (4 to 8) | 0.187 |

* Data between randomization and hospital discharge. Data are presented as numbers and percentages or median and IQR.
† Number of patients included in the analysis.

**Table 4**
Per protocol analyses*.

| | Study group ($n$ = 75) | Control group ($n$ = 86) | $P$ |
|---|---|---|---|
| Per protocol | | | |
| Postoperative blood loss after 12-hour stay in the ICU | 50 (−300 to 375) | 505 (350 to 754) | <0.001 |

* Data between randomization and hospital discharge. Data are presented as median and IQR.

0.21 ± 0.79; $p$ = 0.668) and hospital discharge (−0.48 ± 0.91 vs. −0.45 ± 1.08; $p$ = 0.810) between the study and control group, respectively. The proportion of patients transfused with red cells, fresh frozen plasma, and platelet concentrate after randomization was comparable between groups. There were no significant between-group differences in the median times of chest tube removal ($p$ = 0.477), and the duration of mechanical ventilation ($p$ = 0.187). Median length of stay in the ICU (23 h, IQR 20 to 48 vs. 25 h, IQR 20 to 44; $p$ = 0.756) and total hospitalization after randomization (8 days, IQR 7 to 10 for both groups, $p$ = 0.333) were also comparable between the study and control group, respectively. (Table 3).

### 3.1. Sensitivity analyses

Sensitivity analyses have been performed to adjust for the confounding effects of one significantly different intraoperative variable, patients whom received intraoperative platelets transfusion (0 patients vs. 6 patients $p$ = 0.029). Sensitivity analyses have also been performed to explore the influence of opened pleural cavities and mechanical ventilation duration on 12-hour postoperative blood loss. Result show that after adjustment for these potential confounders, the reduction of postoperative blood loss after 12-hour stay at the ICU remained the same (raw mean treatment effect was 422 ml vs. adjusted treatment effect 415 ml).

### 3.2. Subgroup analysis

In the subgroups with surgically opened pleural cavities, differences in mean reduction of postoperative blood loss increased (Table 5) though this difference between subgroups was not significant ($p$ = 0.061). Results showed that negative postoperative blood loss after 12 h stay at the ICU was associated with the number of surgically opened pleural cavities, in the group with two opened cavities we observed 14 patients with negative postoperative blood loss out of the 25 patients in this subgroup (56%, 95% CI 37% to 75%) versus 18

**Table 5**
Subgroup analyses.

| | Study group | Control group | $P$ | *Dif in mean* |
|---|---|---|---|---|
| **Blood loss at T 12** | | | | |
| Closed pleural cavity (13 − 15) *median and IQR* | 180 (−50 to 350) | 300 (205 to 410) | | |
| One opened pleural cavity (45 − 52) *median and IQR* | 125 (−90 to 525) | 555 (400 to 757) | | |
| Two opened pleural cavities (25 − 19) *median and IQR* | −140 (−585 to 450) | 600 (485 to 863) | | |
| **Blood loss at chest tube removal** | | | | |
| Closed pleural cavity (13 − 15) *median and IQR* | 300 (100 to 730) | 500 (305 to 678) | 0.440 | |
| One opened pleural cavity (45 − 52) *median and IQR* | 540 (100 to 1000) | 740 (545 to 1100) | 0.040 | |
| Two opened pleural cavities (25 − 19) *median and IQR* | 375 (−80 to 700) | 850 (705 to 1295) | 0.001 | |
| **Blood loss at T 12** | | | | |
| Closed pleural cavity (13 − 15) *mean and SD* | 158 ± 635 | 357 ± 185 | 0.294 | 199 ml |
| One opened pleural cavity (45 − 52) *mean and SD* | 233 ± 602 | 606 ± 287 | <0.001 | 373 ml |
| Two opened pleural cavities (25 − 19) *mean and SD* | 18 ± 843 | 649 ± 286 | 0.003 | 631 ml |
| **Blood loss at chest tube removal** | | | | |
| Closed pleural cavity (13 − 15) *mean and SD* | 419 ± 491 | 505 ± 230 | 0.567 | 86 ml |
| One opened pleural cavity (45 − 52) *mean and SD* | 708 ± 848 | 916 ± 562 | 0.166 | 208 ml |
| Two opened pleural cavities (25 − 19) *mean and SD* | 506 ± 903 | 1127 ± 618 | 0.014 | 621 ml |

**Table 6**
Bleeding-related adverse events between randomization and six months follow-up*.

| | Study group (*n* = 83) *Randomization – Hospital discharge* n/total n † | | Control group (*n* = 86) n/total n † | | P | Study group (*n* = 83) *Hospital discharge - Six months follow-up* n/total n † | | Control group (*n* = 86) n/total n† | | P |
|---|---|---|---|---|---|---|---|---|---|---|
| Cardiac tamponade (acute / late) | 83/83 | 0 (0%) | 86/86 | 3 (4%) | 0.246 | 83/83 | 0 (0%) | 86/86 | 3 (4%) | 0.246 |
| Reoperation | | | | | | | | | | |
| For non-surgical bleeding | 83/83 | 0 (0%) | 86/86 | 3 (4%) | 0.246 | 83/83 | | 86/86 | | |
| For surgical bleeding | 83/83 | 4 (5%) | 86/86 | 1 (1%) | 0.205 | 83/83 | | 86/86 | | |
| For other reasons | 83/83 | 0 (0%) | 86/86 | 1 (1%) | 1.000 | 83/83 | | 86/86 | | |
| Minimal invasive intervention for fluid accumulation | | | | | | | | | | |
| Pericardial intervention | 83/83 | 0 (0%) | 86/86 | 1 (1%) | 1.000 | 83/83 | 0 (0%) | 86/86 | 3 (4%) | 0.246 |
| Pleural intervention | 83/83 | 3 (4%) | 86/86 | 0 (0%) | 0.116 | 83/83 | | 86/86 | | |
| Infections† | | | | | | | | | | |
| Sepsis | 83/83 | 1 (1%) | 86/86 | 1 (1%) | 1.000 | 83/83 | | 86/86 | | |
| Pneumonia | 83/83 | 6 (7%) | 86/86 | 9 (11%) | 0.591 | 83/83 | 3 (4%) | 86/86 | 2 (2%) | 0.678 |
| Pericarditis | 83/83 | 5 (6%) | 86/86 | 7 (8%) | 0.766 | 83/83 | 0 (0%) | 86/86 | 1 (1%) | 1.000 |
| Deep sternal wound infection | 83/83 | | | | | 83/83 | 1 (1%) | 86/86 | 1 (1%) | 1.000 |
| Surgical wound infection | 83/83 | | | | | 83/83 | 2 (2%) | 86/86 | 1 (1%) | 0.616 |
| Sternal dehiscence | 83/83 | 1 (1%) | 86/86 | 1 (1%) | 1.000 | 83/83 | | 86/86 | | |
| Delirium | 83/83 | 5 (6%) | 86/86 | 7 (8%) | 0.766 | 83/83 | 0 (0%) | 86/86 | 1 (1%) | 1.000 |
| Acute renal insufficiency | 83/83 | 1 (1%) | 86/86 | 2 (2%) | 1.000 | 83/83 | | | | |
| Postoperative atrial fibrillation | 83/83 | 28 (34%) | 86/86 | 33 (38%) | 0.631 | 83/83 | 2 (2%) | 86/86 | 6 (7%) | 0.278 |
| Myocardial infarction | 83/83 | 2 (2%) | 86/86 | 3 (4%) | 1.000 | 83/83 | | 86/86 | | |
| Mortality | 83/83 | 0 (0%) | 86/86 | 0 (0%) | | 83/83 | 0 (0%) | 86/86 | 0 (0%) | |

* Data is presented as numbers and percentages, unless otherwise specified.
† Number of patients included in the analysis.

patients with negative postoperative blood loss out of the 58 in the subgroup with closed or one opened pleural cavity (31%, 95% CI 19% to 43%).

### 3.3. Adverse events

None of the patients in the study group required reoperation for non-surgical bleeding versus 3 (4%, 95%CI −0,4% to 7%) in the control group (Table 6). Acute cardiac tamponade did not occur in any of the patients in the study group, versus 3 (4%, 95%CI −0,4% to 7%) in the control group. Drainage by pericardial puncture for progressive pericardial effusion during hospitalization was needed in 1 patient in the control group. Interventions for pleural effusion during hospitalization was required in 3 (4%, 95%CI −0,4% to 8%) patients in the study group versus 0 in the control group. Other in-hospital adverse events were comparable between groups.

### 3.4. Cost analysis

Adverse events between hospital discharge and six months follow-up were not significantly different between groups ($p$>0,246). Interventions for pericardial effusion were not required in the study group versus 3 (4%, 95%CI −0,4% to 8%) patients in the control group.

Data for resource use during the primary admission at the study centre was complete but 16 patients who rehabilitated at their referral hospital had missing final discharge dates. The proportion of incomplete EQ-5D and SF-HLQ scores for the first 115 patients was 19%, the last 54 patients did not receive any postoperative questionnaire, thus the proportion of incomplete EQ-5D and SF-HLQ scores was 32%.

The average total cost of resources in the study group was €646 more than in the control group, but this difference was not statistically significant ($p$ = 0.752). The total cost was largely direct medical cost from resource use inside the hospital. Since the average age of study population was above the retirement age, the indirect cost accounted only for a small proportion of the total cost.

The difference in mean EQ-5D before and 6 months after surgery were 0.021 (± 0.193) for the study group and 0.012 (± 0.152) for the control group (Table 7). Between group difference of QoL improvement was 0.0089 ($p$ = 0.806). The baseline characteristics and outcome data were comparable between the group of patients with complete EQ-5D and SF-HLQ data and the group with incomplete

**Table 7**
Cost-utility analysis*,**.

| | n/total n † | Study group (*n* = 83) | n/total n† | Control group (*n* = 86) | P |
|---|---|---|---|---|---|
| **Cost** | | | | | |
| Direct medical cost (hospital) | 76/83 | 10.495 ± 6792 | 75/86 | 9182 ± 6.086 | 0.543 |
| Direct medical cost (outside hospital) | 38/83 | 359 ± 1.062 | 40/86 | 86 ± 271 | 0.119 |
| Indirect cost | 41/83 | 418 ± 2.577 | 47/86 | 761 ± 4.345 | 0.659 |
| Total cost | | 11.404 ± 8.749 | | 10.367 ± 7.812 | 0.752 |
| **Utility** | | | | | |
| pre-op EQ-5D | 82/83 | 0.84 ± 0.20 | 85/86 | 0.86 ± 0.15 | 0.520 |
| post-op EQ-5D | 44/83 | 0.86 ± 0.18 | 49/86 | 0.87 ± 0.13 | 0.830 |
| Δ EQ-5D | | 0.021 ± 0.193 | | 0.012 ± 0.152 | 0.806 |
| **Cost-effect ratio** | | | | | |
| Δ cost (control-study) | | 1037 | | | |
| Δ EQ-5D (control-study) | | 0.009 | | | |
| **ratio** | | **116.513** | | | |

* Cost in €.
** Data is presented mean ± SD, unless otherwise specified.
† Number of patients included in the analysis.

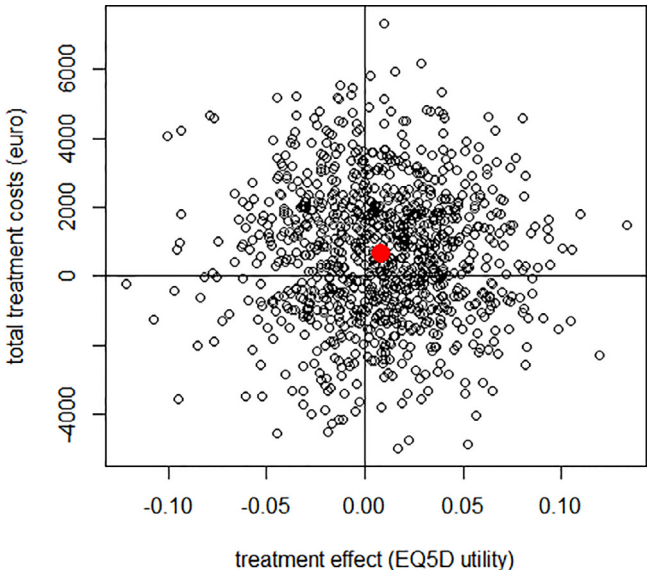


**Fig. 2.** Bootstrap analysis cost-effectiveness ratio.

data, the group with incomplete data had slightly more fresh frozen plasma and platelet concentrate transfusions. The incremental cost-effectiveness ratio was €116.513 (95% bootstrap CI €−882.068 to € +897.278). The bootstrap result is displayed graphically in Fig. 2.

CPPF did not have any adverse or beneficial effect on the patients QoL and it did not lead to incremental cost or cost reduction. The budget impact is limited to the purchase price of the fully automated CPPF device, which is still under development, estimated on €20.000 which will have a marginal impact on the budget.

## 4. Discussion

The CPPF study was a randomized clinical trial investigating the impact of CPPF with a saline solution on postoperative blood loss in the first postoperative hours after coronary artery bypass grafting and cost-effectiveness of this novel therapy. Analysis of the primary outcome showed that median postoperative blood loss after 12-hour stay in the ICU was reduced with 76% in the study group when compared to the control group. Our previous study, amongst adults undergoing non-emergent elective correction for congenital heart disease (CHD) or valvular surgery, showed a reduction of 41%. This study population of younger aged congenital patients with less comorbidities, had a relatively low risk when compared to the CABG population. [7] Moreover, preoperative use of antiplatelet medication, was 97% in the CABG population compared to 60% in the CHD/valve population. Therefore, the difference in postoperative blood loss reduction may be due to the higher bleeding tendency of patients undergoing coronary artery bypass grafting, possibly leading to a more distinctive treatment effect in this group; 475 ml (50 to 925) in the study group versus 725 ml (517 to 1052) in the control group.

As in our previous study, we observed virtual negative postoperative blood loss in a proportion of the study group, leading to overestimation of the result regarding the primary end point. An important part of the negative blood loss is caused by the delay in time between the infusion fluid to enter the patient, where it sometimes accumulates for a certain time before it comes out. The incidence of negative blood loss is therefore much less pronounced at the time of chest tube removal (Table 3). We anticipated on the possibility of fluid retention and incorporated pre-specified sensitivity analyses on the number of surgically opened pleural cavities. In the subgroups with surgically opened pleural cavities, results show that negative postoperative blood loss after 12 h stay at the ICU was associated with the number of surgically opened pleural cavities; in the group with two opened cavities we observed 14 patients with negative postoperative blood loss out of the 25 patients in this subgroup (56%, 95% CI 37% to 75%) versus 18 patients with negative postoperative blood loss out of the 58 in the subgroup with closed or one opened pleural cavity (31%, 95%CI 19% to 43%). It is possible that the CPPF irrigation fluid absorption capacity in the subgroup with two opened pleural cavities is increased, due to the larger pleural and mediastinal epithelial surface. As a significant intrapericardial fluid accumulation was observed in only one patient in the study group, it is unlikely that the CPPF irrigation fluid accumulates in the pleural and pericardial cavity. Nevertheless, postoperative blood loss was underestimated in the study group since negative postoperative blood loss is non-existent post-cardiac surgery. Real time measurement of the blood content (hematocrit value) of the outflow volume can eliminate this problem. Therefore, we conclude that future clinical trials and more importantly implementation of CPPF therapy in the clinical setting, should only be done with real time hematocrit analysis of the MCTD. Only in this way one can be assured of an accurate measurement of postoperative bleeding at any time, which is essential for clinical decision making.

Besides this, it is very likely that in a number of patients in the control group certain amounts of blood and clots were retained in the opened body cavities, with no direct clinical manifestations but also leading to an underestimation of postoperative blood loss. The fact is that retained blood post cardiac surgery is a clinical entity well recognized in literature [15] and also the rationale for this study. The choice for postoperative blood loss as primary outcome was based on pilot study findings [12] and under the assumption that postoperative blood loss reduction would demonstrate clinical effectiveness at the smallest sample size, whereas most retained blood-related acute adverse events have a relatively low incidence rate of only a few percentage points. For example, re-exploration for acute cardiac tamponade or non-surgical bleeding did not occur in the study group versus 6 times in the control group. Although not statistically different due to the small sample size, this result underlines the proof of concept of CPPF therapy. This is also confirmed by the findings of our previous study, were reoperation for acute cardiac tamponade or non-surgical bleeding did not occur under CPPF treatment. [7]

No significant differences in hemoglobin levels were found between the time of randomization, after 12 h of CPPF and before discharge. However, hemoglobin levels are strongly dependent on other factors like total water content of the body, total of fluids infused, body weight, prime volume of the heart-lung machine and the use of diuretics. A difference in blood loss of only a few hundred ml's is very difficult to trace in hemoglobin level unless in high inclusion numbers or in combination with very strict fluid balance and red cells transfusion protocol. All patients admitted for cardiac surgery drop around 2,5 g/dL, independent of their amount of blood loss.

There were no significant differences in pleural or pericardial fluid accumulations at discharge. Three patients in the study group had a chest tube replaced during primary hospitalization over none in the control group. One patient had a pneumothorax after chest tube removal and the other patient had a right sided hydro-pneumothorax requiring drainage by chest tube replacement, although the right pleural cavity was not opened during surgery, therefore a causal relationship with the CPPF therapy seems unlikely. The third patient requiring pleural re-intervention had multiple complications, and was readmitted with a pneumonia and sternal dehiscence.

We did not expect to find significant differences in QoL improvement as a result from CPPF, before and after surgery, since cardiac surgery alone is known to produce a marked increase in QoL within months of the procedure [16], the limited improvements that we observed must be attributable to the conventional cardiac operation. Given the clinical results of this study, it is perhaps not surprising that the per-patient costs were not statistically different for the study group compared to the control group. With comparable costs and no

improvement in QoL during the 6 months of the study, cost consideration for the implementation of CPPF would not be relevant.

Conventional methods to maintain chest tube patency, like milking, stripping and open suction, have never been proven effective and even may be harmful. [17, 18] Besides CPPF there are two important other techniques that aim for improved pericardial drainage. They have the same purpose to reduce postoperative complications that are the consequence of retained blood. Posterior pericardial drainage is the first and was evaluated in a systematic review and meta-analysis over 19 randomized controlled trials. [2] It was shown that this technique significantly reduces not only the prevalence of early pericardial effusion and postoperative atrial fibrillation but also late pericardial effusion and cardiac tamponade. These benefits also translate into improved survival after heart surgery. [2] Secondly, active tube clearance (ATC) has also shown impressive results in several studies [19–26], although we are still awaiting confirmation of the results in a randomized clinical trial.

Our study has some limitations. Because of the inevitable unblinded study design, the involved caregivers were aware of treatment-group assignment, which may lead to biased decision making in the postoperative period Secondly, the phenomenon of negative postoperative blood loss on the primary outcome needs to be further investigated and clarified before we can draw final conclusions about the degree of postoperative blood loss reduction.

In conclusion, this study indicates that CPPF may be an effective method to reduce postoperative blood loss after cardiac surgery. Real time hematocrit analysis of MCTD will become essential to overcome the problem of inaccurate measurement of blood loss, which is necessary for clinical decision making and implementation of CPPF in a clinical setting.

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## Data sharing

For purposes of reproducing the results or replicating the method, the corresponding author will make the data, analytic methods, and study materials available to other researchers on request, with investigator support.

## Contributors

JM, DK, designed the study, wrote the study protocol, performed the power calculation. CdB provided expert methodological and clinical feedback on study protocol and participated in writing of study protocol. AZ reviewed the data analyses, interpretation of the results, and participated in writing of the manuscript. JH provided expert clinical perspective on study design, interpretation of the results, and writing of the manuscript. JW, interpretation of the results, and writing of the manuscript. WJvB, interpretation of the results, and writing of the manuscript. SE, interpretation of the results, and writing of the manuscript. NJ, interpretation of the results, and writing of the manuscript. MS, interpretation of the results, and writing of the manuscript. JM an ED were primary responsible for inclusion of study participants, execution of study, and data collection. The draft manuscript was written jointly by ED and DK, and all the authors worked collaboratively to prepare the final content and made the decision to submit the manuscript for publication.

## Declaration of Competing Interest

Based on the experiences from this study and for the safe application of the CPPF therapy, author DK invented and patented a new medical device (WO2015086857A1). ED has received personal fees outside the submitted work from Haermonics B.V. during 2018. Authors DK and ED are members of a start-up company (Haermonics B.V.) that will develop this device. In this capacity they may have future benefits from this. All other authors have nothing to declare.

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## Abbreviations and acronyms

Amsterdam UMC = Amsterdam University Medical Center, Amsterdam, the Netherlands; ATC = active tube clearance; CABG = coronary artery bypass grafting; CHD = congenital heart disease; CI = confidence interval; CONSORT = CONsolidated Standards Of Reporting Trials; CPPF = continuous postoperative pericardial flushing; ICER = incremental cost-effectiveness ratio; ICU = intensive care unit; IQR = interquartile range; LVAD = left ventricular assist device; MCTD = mediastinal chest tube drainage; MEC = medical ethics committee; NTR = Nederlands trial register; PE = pericardial effusion; PP = per protocol; QoL = quality of life; RBC = retained blood syndrome; CT = randomized controlled trial; SAP = statistical analysis plan; SD = standard deviation; SF-HLQ = Short Form- Health and Labour Questionnaire; SPSS = Statistical Package for the Social Sciences; TTE = Transthoracic echocardiography; ZonMw = Zorgonderzoek Medische Wetenschappen

## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2020.100661.

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