An open randomized controlled trial of median sternotomy versus anterolateral left thoracotomy on morbidity and health care resource use in patients having off-pump coronary artery bypass surgery: The Sternotomy Versus Thoracotomy (STET) trial

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Objective: Our objective was to compare off-pump coronary artery bypass surgery carried out via a left anterolateral thoracotomy (ThoraCAB) or via a conventional median sternotomy (OPCAB).

Background: Recent advances in minimally invasive cardiac surgery have extended the technique to allow complete surgical revascularization on the beating heart via thoracotomy.

Methods: Patients undergoing nonemergency primary surgery were enrolled between February 2007 and September 2009 at 2 centers. The primary outcome was the time from surgery to fitness for hospital discharge as defined by objective criteria.

Results: A total of 93 patients were randomized to off-pump coronary artery bypass surgery via a median sternotomy (OPCAB) and 91 to off-pump coronary artery bypass surgery via a left anterolateral thoracotomy (ThoraCAB). The surgery was longer for patients in the ThoraCAB group (median, 4.1 vs 3.3 hours) and there were fewer with more than 3 grafts (2% vs 17%). The median time from surgery to fitness for discharge was 6 days (interquartile range, 4-7) in the ThoraCAB group versus 5 days (interquartile range, 4-7) in the OPCAB group ($P = .53$). The intubation time was shorter, by on average 65 minutes, in the ThoraCAB group ($P = .017$), although the time in intensive care was similar ($P = .91$). Pain scores were similar ($P = .97$), but more analgesia was required in the ThoraCAB group (median duration, 38.8 vs 35.5 hours, $P < .001$; tramadol use, 66% vs 49%, $P = .024$). ThoraCAB was associated with significantly worse lung function at discharge (average difference, –0.25 L, $P = .01$) but quality of life scores at 3 and 12 months were similar ($P = .52$). The average total cost was 10% higher with ThoraCAB ($P = .007$).

Conclusions: ThoraCAB resulted in no overall clinical benefit relative to OPCAB. (J Thorac Cardiovasc Surg 2013;146:306-16)

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Minimally invasive cardiac surgery (MICS) aims to reduce the inflammatory response, organ dysfunction, and morbidity attributable to surgical access, cardiopulmonary bypass (CPB), and manipulation of the aorta, while achieving complete revascularization. Minimally invasive direct coronary artery bypass (MIDCAB) via a left anterior small thoracotomy represented a milestone development, conferring the survival benefit of the left internal thoracic artery to the left anterior descending artery while avoiding sternotomy and CPB.[1-3] The technique was then extended to patients with multivessel disease by combining MIDCAB with percutaneous coronary intervention to non–left anterior descending artery vessels to provide truly minimally invasive hybrid multivessel revascularization.[4,5] However, hybrid procedures were only possible in selected patients with favorable anatomy. Moreover, logistical issues remained, and the reintervention rate was high.[6-8] Rather, MIDCAB led to renewed interest in off-pump coronary artery bypass (OPCAB) where complete revascularization could be achieved without CPB and often without aortic manipulation, albeit via a sternotomy incision.[9,10] In

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Abbreviations and Acronyms

CABG = coronary artery bypass graft
CI = confidence interval
CPB = cardiopulmonary bypass
FEV_1 = forced expiratory volume after 1 second
FVC = forced vital capacity
IL = interleukin
MICS = minimally invasive cardiac surgery
MIDCAB = minimally invasive direct coronary artery bypass
OPCAB = off-pump coronary artery bypass surgery via a median sternotomy
RCT = randomized controlled trial
SIRS = systemic inflammatory response syndrome
ThoraCAB = off-pump coronary artery bypass surgery via a left anterolateral thoracotomy
TR = time ratio

randomized controlled trials (RCTs), OPCAB reduced the inflammatory response and severity of organ injury and used fewer health care resources,[11] with equivalent long-term graft patency, quality of life, and survival compared with coronary artery bypass grafting (CABG) with CPB.[12,13]

The increasingly high-risk population referred for surgery, the morbidity associated with sternotomy, economic considerations, and the desires of patients for less postoperative pain and a quicker return to normal living have led to pressure to further refine MICS techniques. To extend the advantages of OPCAB, several groups have developed a technique whereby complete revascularization may be performed on the beating heart through a lateral thoracotomy incision (ThoraCAB) with minimal morbidity and rapid hospital discharge.[14-16] Concerns remain, however, as to whether in unselected patients technical precision may be compromised[3] or whether excessive rib retraction may result in increased postoperative pain.[17] We carried out an RCT to evaluate whether ThoraCAB represents a clinical benefit beyond that conferred by OPCAB.

METHODS

Study Design

A 2-center, open, parallel-group RCT (ISRCTN 77366282) was used.

Participants

Participants included adults (>16 years and <80 years) undergoing nonemergency primary CABG on the beating heart without the use of CPB and cardioplegic arrest. Patients who had undergone heart or lung surgery previously or for whom the surgeon was unwilling to carry out the surgery via either method were excluded.

Study Settings

The study was conducted at the Bristol Heart Institute, Bristol (United Kingdom) and Ospedale Pasquinucci, Massa Carrara (Italy), 2 specialized regional cardiac surgery centers. Three surgeons, 2 in Bristol and 1 in Italy, participated. The study was approved by the Southmead Research Ethics Committee (ref. 07/Q2002/53) and by the Comitato Etico Locale of the Ospedale Pasquinucci (protocol number 150).

Interventions

Patients were randomized to CABG on the beating heart through either a median sternotomy (OPCAB, control) or a left anterolateral thoracotomy (ThoraCAB, experimental). OPCAB was carried out as described previously[9] with subsequent modifications subsumed into the current standard protocol, for example, use of an intracoronary shunt when performing a distal anastomosis. ThoraCAB, and associated anesthetic technique, was carried out as described by Guida and colleagues.[14] With the left side of the patient elevated to approximately 30°, an anterolateral incision is made on the fourth or fifth intercostal space from the midclavicular to the anterior axillary line, sparing the latissimus dorsi. The left lung is usually deflated; if single lung ventilation is not possible, the left lung is gently compressed using a laparotomy sponge. The left internal thoracic artery is harvested under direct vision. The pericardium is incised from the pulmonary artery toward the ascending aorta and then toward the right atrial appendage. Traction sutures are positioned on the pericardium to rotate the ascending aorta to the right side. Proximal graft anastomoses on the aorta are performed first with a side-biting clamp in the conventional way. The pericardium is then incised parallel to the left phrenic nerve to expose the posterior and lateral wall vessels. Distal anastomoses are performed with an Octopus stabilizer (Medtronic Inc, Minneapolis, Minn) and intracoronary shunt.

Postoperative management was in accordance with institution-specific protocols. A protocol for postoperative pain relief for ThoraCAB patients was written by cardiac anesthetists and intensivists in Bristol. A policy of early extubation was adopted for all patients. For ThoraCAB patients, at the time of wound closure the surgeon sutured in place a paravertebral catheter to provide a paravertebral block (infusion of 0.125% bupivacaine, 5-10 mL/h); a 15- to 20-mL loading bolus of 0.25% bupivacaine through the catheter and injections into the intercostal spaces (0.125% bupivacaine) were also given before chest closure. Pain relief in the event of failure of the paravertebral catheter included the following: (1) local analgesia, intercostal blocks, up to 6 spaces injecting 5 mL 0.125% bupivacaine into each space, repeated 4 to 6 hourly if required; (2) adjuvant analgesia, intravenous ketoralac/diclofenac (up to 30 mg); (3) adjuvant analgesia, nurse administered intravenous morphine (up to 5-mg boluses); and (4) adjuvant analgesia, intravenous ketamine infusion (1.5-3 $\mu g \cdot kg^{-1} \cdot min^{-1}$). All patients had patient-controlled analgesia.

Outcome Measures

Primary outcome. The primary outcome was the number of days from surgery until fit for discharge from the hospital. Patients were classified fit when (1) the chest x-ray film was clear with no evidence of pleural effusion requiring drainage, lung collapse/consolidation, or pneumothorax, (2) there was no suspected infection, (3) routine blood test results and temperature were normal, and (4) the patient was physically fit.

The definition was modified partway through the trial after feedback from the independent Data Monitoring and Safety Committee. Initially, components 3 and 4 were *not* included. These data were collected retrospectively for the Bristol patients recruited before the change but were not available for the Italian patients. The definitions applied to minimize the susceptibility to detection bias are described in Appendix E1.

Secondary outcomes. Secondary outcomes were as follows: (1) the patient's judgment about his or her readiness for discharge; (2) biochemical inflammatory markers, that is, complement activation (C3a and C5) and interleukin (IL-6, IL-8, and IL-10)[18] assessed preoperatively, at the end of the operation, and 4, 12, and 24 hours postoperatively; (3) pulmonary function

tests at recruitment and discharge; (4) pain scores measured with a 10-cm visual analog scale at 2, 12, 24, and 36 hours after extubation and on discharge; (5) the total volume and dose of local anesthetic (paravertebral block), patient-controlled analgesia, and other intravenous analgesia administered; use of nonsteroidal anti-inflammatory or opioid drugs; (6) length of intensive care unit and postoperative hospital stay; (7) in-hospital mortality and other standard measures of morbidity as used in previous RCTs[9]; (8) including ASEPSIS* at 6 weeks postoperatively[19]; (9) use of health care resources and associated costs; and (10) quality of life at recruitment and 3 and 12 months after surgery, measured using the coronary revascularization outcome questionnaire.[20] Pulmonary function tests included peak expiratory flow rate, forced vital capacity (FVC), forced expiratory volume after 1 second (FEV_1) and the FEV_1/FVC ratio. If a patient was unable to use the visual analog scale, a verbal response was requested.

Costs associated with health care resource use included staffing and overheads (1) in the theater for the duration of the operation, (2) during the intensive care, high dependency, and postoperative ward stay, (3) additional operative interventions to treat complications, and (4) readmissions. Costs were limited to the perspective of the United Kingdom National Health Service; information was not collected from participants (see Appendix E1).

Data on pulmonary function, postdischarge wound infections, and quality of life were collected for the Bristol patients only. Biochemical inflammatory markers were assessed in a consecutive subsample of 60 Bristol patients.

Sample Size

Inasmuch as no published data existed for time until fit for discharge, information about total postoperative hospital stay was used as a proxy. The 2 published case series for ThoraCAB reported 63% discharged within 4 days[15] and 65% discharged within 2 days.[14] The median postoperative stay after OPCAB in Bristol was 6 days, with 69% discharged within 7 days. We suspected that the ThoraCAB data were optimistic and so set the sample size to detect median times until fit for discharge of 3 and 5 days, respectively (assuming time until fit for discharge would be shorter, on average, than the total postoperative stay). A study of 180 patients (90 per group) had 90% power to detect this difference (hazard ratio, 1.65) with 5% significance (2-tailed).

Randomization

Randomized treatment allocations were computer generated.[21] Allocations were stratified by center and cohort minimization was used to ensure balance for the number of diseased vessels, diabetic status, and surgeon. Patients were assigned in a 1:1 ratio. The Internet-based system was password protected and allocations were concealed until data to uniquely identify the patient and confirm eligibility had been entered.

Statistical Methods

The time until fit for discharge was determined from the individual fitness criteria. A patient was classified fit on the earliest date after surgery when all the criteria were met (and no component event subsequently recurred before discharge). If any of the component events were not "resolved" during the patient's postoperative hospital stay (ie, the patient was discharged with 1 "event" or more present), then the patient's fitness was censored at the time of discharge from the cardiac unit. Similarly, if at least 1 of the criteria was not met before discharge and was not subsequently reassessed, then the outcome was censored at the time of this last assessment. For patients recruited in Italy before the fitness definition was changed, the actual length of postoperative hospital stay was used. If the time to extubation or discharge was not observed because the patient died, the outcome was censored at death.

Analyses were carried out on the basis of intention to treat. Continuous variables were summarized using the mean and standard deviation (or median and interquartile range if the distribution was skewed), and categorical data were summarized as a number and percentage. All comparisons of outcomes between the OPCAB and ThoraCAB patients were adjusted for factors included in the cohort minimization. Results are presented as effect sizes with 95% confidence intervals (CIs).

One subgroup analysis, comparing the primary outcome for patients with and without pre-existing diabetes, was prespecified. This was examined by adding a diabetes-by-treatment interaction term to the model.

Sensitivity analyses were performed for the primary outcome (see Appendix E1).

Further detail on the statistical methodology used is given in Appendix E1.

RESULTS

Patient Recruitment

Patients were recruited from February 2007 to September 2009; 191 patients were enrolled, with 95 being allocated to ThoraCAB and 96 to OPCAB (Figure 1).

Protocol Violations

There were 20 protocol violations in 18 patients. Eight patients allocated to ThoraCAB had operations via OPCAB and 1 patient allocated to OPCAB had the operation via ThoraCAB. There were 11 conversions to on-pump surgery, 2 in the ThoraCAB group and 9 in the OPCAB group. Reasons for these protocol violations are given in Appendix E1. One patient, randomized to OPCAB, withdrew 3 days after surgery but agreed to the data being used.

Baseline Characteristics and Operative Details

Patient demographics and operative characteristics are presented in Table 1. The duration of surgery was, on average, 50 minutes longer for patients in the ThoraCAB group and fewer patients in the ThoraCAB group had more than 3 grafts.

Numbers Analyzed

Of the 191 patients enrolled, 184 were included in the analyses. Reasons for exclusion included the following: the surgery was postponed and they were subsequently transferred to a surgeon not participating in STET (n = 2), additional left ventricular remodeling was required (n = 2), and no trial data were submitted (n = 3).

Primary Outcome

In the OPCAB group 77% of patients were classified as fit at or before hospital discharge compared with 68% in the ThoraCAB group. For the remaining patients the time to fitness was censored. The observed median time from surgery to fitness for discharge was 6 days (interquartile range, 4-7 days) in the ThoraCAB group versus 5 days (interquartile range, 4-7 days) in the OPCAB group. The estimated time ratio (TR; ThoraCAB/OPCAB) was 1.03 (95% CI, 0.94-1.14; $P = .53$), suggesting the time until fit for discharge was on average 3% longer in the ThoraCAB group.

* ASEPSIS = Additional treatment, the presence of Serous discharge, Erythema, Purulent exudate, and Separation of the deep tissues, the Isolation of bacteria, and the duration of inpatient Stay.

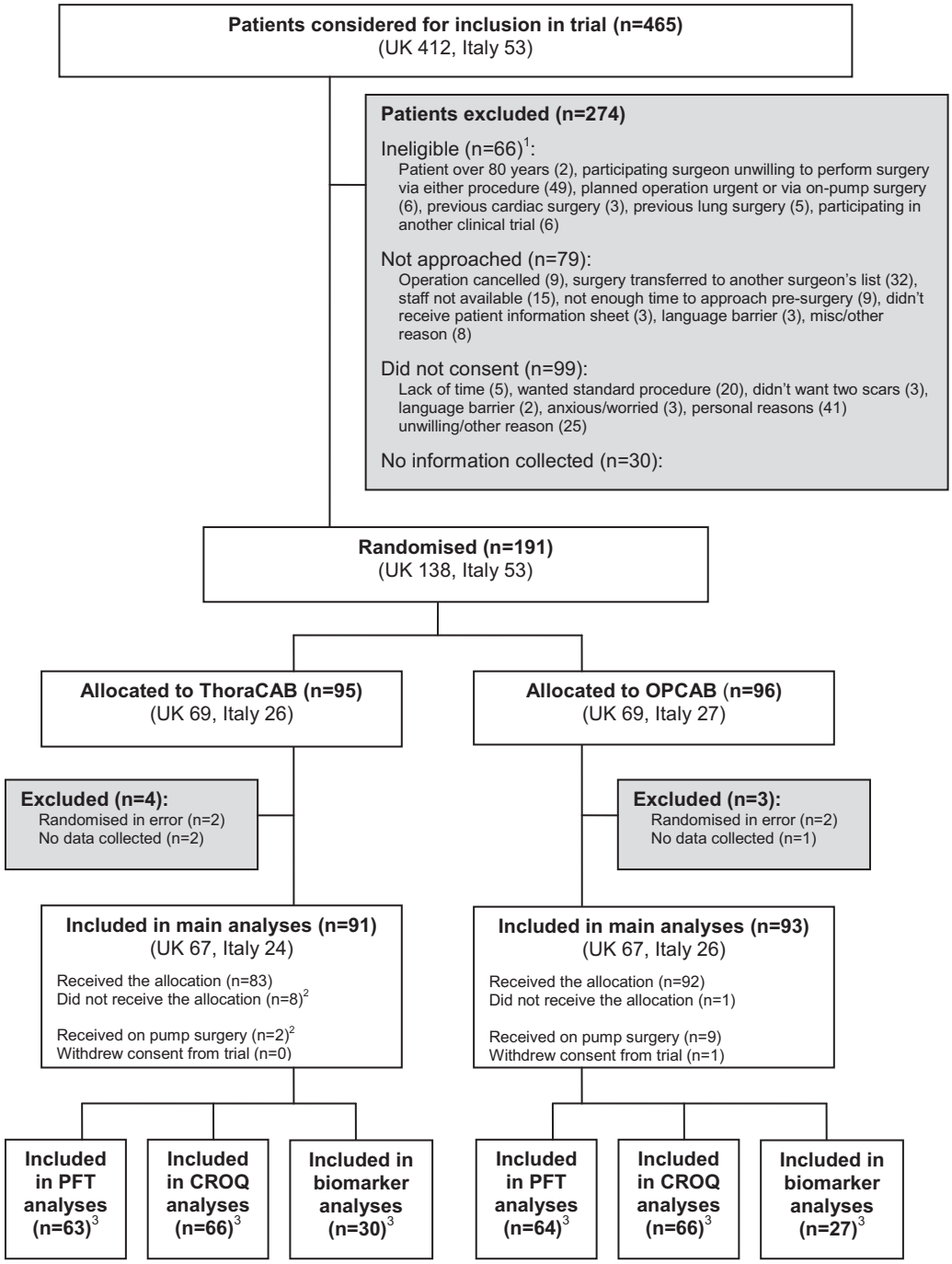

FIGURE 1. Flow diagram of the progress through the phases of the trial. Notes: (1) Some patients were ineligible for more than 1 reason. (2) The 2 patients who received on-pump surgery also did not receive their treatment allocation. (3) Only patients from the United Kingdom (*UK*) are included in these cohorts. *ThoraCAB*, Off-pump coronary artery bypass surgery via a left anterolateral thoracotomy; *OPCAB*, off-pump coronary artery bypass surgery via a median sternotomy; *PFT*, pulmonary function test; *CROQ*, Coronary Revascularization Outcome Questionnaire

Figure 2, *A*, shows the time to fitness for discharge by treatment group.

Secondary Outcomes

Postoperative clinical outcomes. Secondary clinical outcomes are reported in Table 2. The intubation time was shorter, by on average 65 minutes, for patients in the ThoraCAB group, although the time in intensive care and in the hospital was similar (Figure 2, *B* and *C*) There were fewer arrhythmias in the ThoraCAB group, but other complications occurred with similar frequency. Total mediastinal fluid loss was on average 30% higher in the ThoraCAB

TABLE 1. Patient demography, history, and operative data

	Randomized to ThoraCAB (n = 91)		Randomized to OPCAB (n = 93)		Overall (n = 184)	
	n	%	n	%	n	%
Demography						
Age (y)						
Mean (SD)	63.1 (8.7)		66.7 (8.0)		64.9 (8.5)	
Sex						
Male	84	92	80	86	164	89
BMI						
Mean (SD)	27.6 (4.1)		28.0 (3.9)‡		27.8 (4.0)	
Cardiac history						
NYHA						
I/asymptomatic	48	53	44†	48	92	51
II	29	32	35	38	64	35
III	12	13	10	11	22	12
IV	2	2	2	2	4	2
CCS						
No angina	16	18	10†	11	26	14
I	16	18	14	15	30	16
II	37	41	41	45	78	43
III	18	20	17	19	35	19
IV	4	4	9	10	13	7
Q-wave myocardial infarction	27	30	26‡	29	53	29
Congestive cardiac failure	1	1	0†	0	1	1
Concomitant valvular disease	0	0	0†	0	0	0
Other cardiac history	7	8	0†	0	7	4
Heart rhythm						
Sinus	89*	99	89*	97	178	98
Family history	55	60	47§	53	102	57
Left ventricular function						
Good	72*	80	69†	76	141	78
Moderate	17	19	18	20	35	19
Poor	1	1	4	4	5	3
No. of vessels						
Triple	60	66	59	63	119	65
LMS disease						
>50% stenosis	29*	32	43*	47	72	40
Euroscore						
Median (IQR)	3 (1, 4)*		3 (2, 4)‖		3 (2, 4)	
Noncardiac history						
Smoking status						
No	36	40	35‡	39	71	39
Ex-smoker >1 mo	36	40	42	47	78	43
Yes	19	21	13	14	32	18
Diabetes	20	22	24	26	44	24
Hypertension	66	73	75†	82	141	77
Hypercholesterolemia	77	85	72‡	80	149	82
Hypothyroidism	2	2	7§	8	9	5
Peptic ulcer	2	2	3‡	3	5	3
CVA/TIAs	4	4	2	2	6	3
Peripheral vascular disease	2	2	6§	7	8	4
Other medical condition	35†	39	27§	30	62	35
Operative priority						
Urgent	20	22	28†	31	48	26

(Continued)

TABLE 1. Continued

	Randomized to ThoraCAB (n = 91)		Randomized to OPCAB (n = 93)		Overall (n = 184)	
	n	%	n	%	n	%
Preoperative Tests						
Creatinine (μmol/L)						
Mean (SD)	92.9 (18.5)‖		93.1 (27.1)§		93.0 (23.2)	
Hemoglobin (g/dL)						
Mean (SD)	14.4 (3.1)†		13.9 (1.5)‡		14.1 (2.5)	
Platelets ($\times 10^9$/L)						
Mean (SD)	236 (62)†		241 (73)‡		239 (68)	
Oxygen saturation (%)						
Median (IQR)	97.0 (96, 98)¶		97.5 (96, 98)¶		97 (96, 98)	
Mobility						
Able to walk 70 m	68#	99	64#	89	132	94
Drugs on admission						
Diuretics	19†	21	14†	15	33	18
Beta-blockers	75	82	66†	73	141	77
Calcium antagonists	36‡	41	36†	40	72	40
Oral nitrates	16	18	18‡	20	34	19
Heparin until operation	22	24	25†	27	47	26
ACE inhibitor	58	64	55†	60	113	62
Statins	81	89	79†	87	160	88
Aspirin	75	82	83‡	92	158	87
Days preoperative aspirin stopped						
Median (IQR)	3 (1, 6)*		2 (1, 5)		3 (1, 5)	
Clopidogrel	18	20	22†	24	40	22
Days preoperative clopidogrel stopped						
Median (IQR)	8 (6, 11)		7 (3, 8)		7 (5, 10.5)	
Other drugs	45*	50	52†	57	97	54
Operative data in theater						
Operation duration (h)						
Median (IQR)	4.1 (3.5, 4.7)		3.3 (3.0, 4.0)		3.7 (3.2, 4.5)	
No. of grafts						
1	3‡	3	4*	4	7	4
2	41	47	41	45	82	46
3	42	48	31	34	73	41
>3	2	2	16	17	18	10
Lowest core temperature (°C)						
Mean (SD)	35.3 (0.61)		35.1 (0.83)†		35.2 (0.73)	
Lowest hematocrit (%)						
Mean (SD)	35.9 (4.5)†		34.1 (5.8)†		35.0 (5.3)	
Tranexamic acid	72	79	73†	80	145	80
Cell salvage	54	59	43‡	48	97	54
Red blood cell transfusion**	0	0	2†	2	2	1
Other blood products††	1	1	0†	0	1	1
Arrythmias on chest closure‡‡	2†	2	1‡	1	3	2
Defibrillation	4	4	3†	3	7	4
Pacing	1	1	0†	0	1	1
Inotropes (including norepinephrine)	3	3	5†	5	8	4
Vasodilators	7	8	21†	23	28	15
IABP	1	1	1†	1	2	1
On return to intensive care unit						
Temperature (°C)						
Mean (SD)	35.9 (0.96)		35.7 (0.74)		35.8 (0.86)	

(Continued)

TABLE 1. Continued

	Randomized to ThoraCAB (n = 91)		Randomized to OPCAB (n = 93)		Overall (n = 184)	
	n	%	n	%	n	%
Hematocrit (%)						
Mean (SD)	35.6 (4.9)		32.3 (4.4)*		33.9 (4.9)	
Lactate (mmol/L)						
Median (IQR)	1.1 (0.9, 1.5)		1.3 (1.0, 1.7)*		1.2 (0.9, 1.6)	
First 24 hours postoperatively						
Nadir hemoglobin (g/dL)						
Mean (SD)	11.3 (1.5)		10.7 (2.1)†		11.0 (1.8)	
Nadir hematocrit (%)						
Mean (SD)	33.7 (4.6)		31.2 (4.5)		32.4 (4.7)	
Nadir MABP (mm Hg)						
Mean (SD)	64.7 (12.4)		64.2 (11.3)		64.5 (11.8)	
Highest lactate (mmol/L)						
Median (IQR)	1.8 (1.4, 2.4)		1.9 (1.4, 2.5)		1.8 (1.4, 2.5)	

ThoraCAB, Off-pump coronary artery bypass surgery via a left anterolateral thoracotomy; *OPCAB,* off-pump coronary artery bypass surgery via a median sternotomy; *SD,* standard deviation; *BMI,* body mass index; *NYHA,* New York Heart Association; *CCS,* Canadian Cardiovascular Society; *LMS,* left main stem; *IQR,* interquartile range; *CVA,* cerebrovascular accident; *TIA,* transient ischemic attack; *ACE,* angiotensin-converting enzyme; *IABP,* intra-aortic balloon pump; *MABP,* mean arterial blood pressure. *One patient with missing data. †Two patients with missing data. ‡Three patients with missing data. §Four patients with missing data. ||Five patients with missing data. ¶Missing for 65 in ThoraCAB group and 63 in OPCAB group (not collected for earlier part of trial). #Missing for 22 in ThoraCAB group and 21 in OPCAB group (not collected at Italian center for earlier part of trial). **Both patients received 2 units. ††One patient received fresh frozen plasma (2 units). ‡‡All arrhythmias were atrial fibrillation.

group. This was related to the paravertebral block inasmuch as drainage invariably stopped once the anesthetic infusion was discontinued.

Adverse events. The frequencies of adverse events were similar in the 2 groups (Tables E1-E3). There were 2 deaths in the OPCAB group after discharge from the hospital. There were 2 unexpected serious adverse events in patients given ThoraCAB, which were classified as related to the trial intervention. These were a left heart hernia through the thoracotomy wound requiring repair (definitely related) and an acute type A aortic dissection (probably related).

Pain relief and pain scores. On average, the duration of patient-controlled analgesia was 37% longer for patients in the ThoraCAB group, but the total administered dose was similar (Table 2). Complications related to paravertebral block were rare (11 cases, Table E4). Pain scores reduced over time and were similar in the 2 groups (Table 2).

Pulmonary function tests. At hospital discharge, both the mean FEV_1 and mean FVC were higher in the OPCAB group, but the peak expiratory flow and FEV_1/FVC ratio were similar (Table 3).

Biochemical inflammatory markers. For IL-6, lower average concentrations in the ThoraCAB group were observed at 4 hours (ratio, 0.72; 95% CI, 0.53-0.99; $P = .05$), but at other time points the response was similar. For IL-8, the response was, on average, 18% lower in the ThoraCAB group (ratio, 0.82; 95% CI, 0.68-0.99; $P = .044$) while for IL-10 and C5a the response was similar (ratio, 1.04; 95% CI, 0.80-1.35; $P = .77$; and ratio, 1.09; 95% CI, 0.97-1.22; $P = .12$, respectively). For C3a, the treatment effect varied with time, but there was no significant difference between the groups at any individual time point (Table E5).

Hospital resource use and costs. On average, the cost of ThoraCAB was approximately 10% higher than the cost of OPCAB (ratio, 1.10; 95% CI, 1.02-1.18; $P = .007$; Table E6). This was due to longer operation times, more reoperations, and the higher cost of hospital readmissions.

Quality of life scores. On all scales (core total centred on 50 with an SD of 10; scores for all other dimensions scaled from 0 to 100), higher scores indicated better quality of life. Scores did not differ significantly between the groups and there was no evidence of treatment-by-time interactions (Table E7). The average difference in core total score between the ThoraCAB and OPCAB groups was –0.47 (95% CI, –1.94 to 0.99; $P = .52$).

Sensitivity Analyses of Time Until Fit for Discharge

The sensitivity analyses did not alter the conclusion (see Appendix E1).

Subgroup Analysis of Fitness for Discharge

The data suggested a potentially greater treatment difference in favor of OPCAB for the subgroup with pre-existing diabetes (TR, 1.19; 95% CI, 0.97-1.46; $P = .093$) than for the nondiabetic subgroup (TR, 0.99; 95% CI, 0.89-1.11; $P = .86$), but the interaction of diabetes with treatment was not statistically significant ($P = .12$).

DISCUSSION

Main Findings

In this 2-center RCT, ThoraCAB was not associated with a reduced time until fit for hospital discharge relative to OPCAB. The benefits of ThoraCAB, including reduced levels of proinflammatory cytokines, earlier extubation, and fewer postoperative arrhythmias, were offset by longer operation

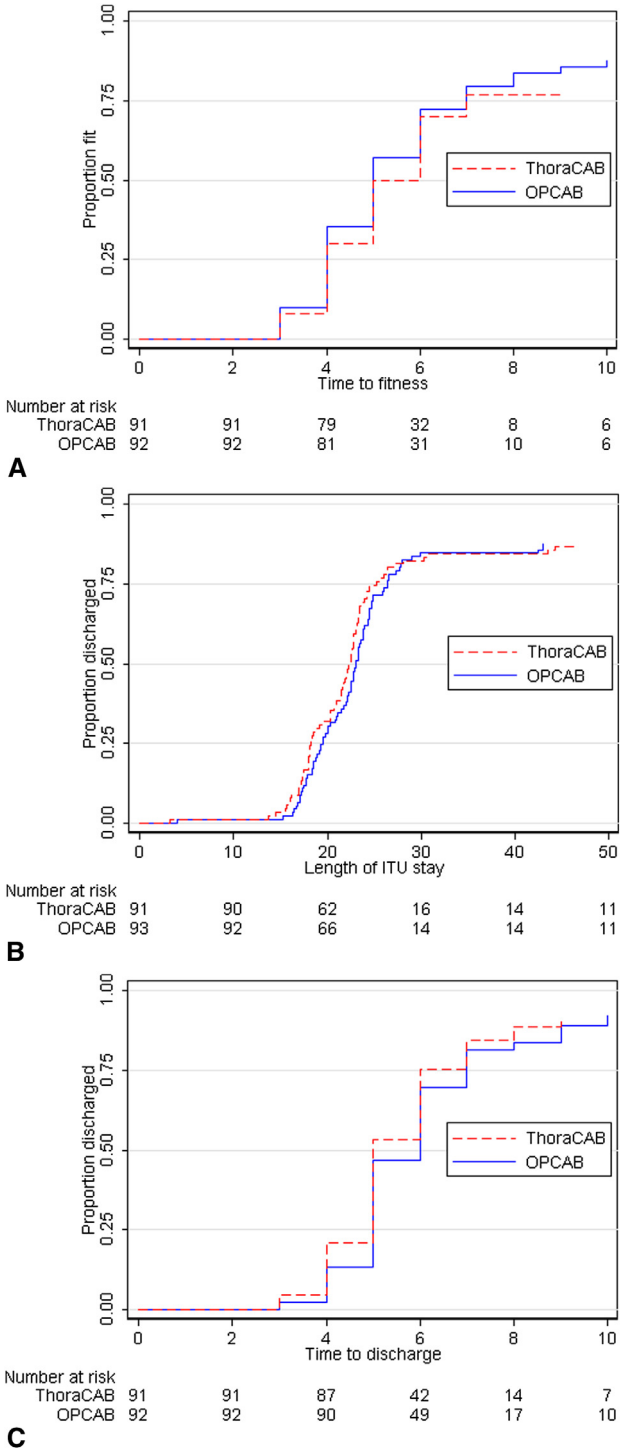

FIGURE 2. Time from surgery to (A) fitness for discharge, (B) discharge from intensive treatment unit *(ITU),* and (C) discharge from hospital. *ThoraCAB,* Off-pump coronary artery bypass surgery via a left anterolateral thoracotomy; *OPCAB,* off-pump coronary artery bypass surgery via a median sternotomy.

times, fewer distal anastomoses on average, greater analgesia requirements, significantly worse lung function at discharge, a higher reoperation rate (4 vs 0 cases), and increased cost. The only in-hospital death was also in the ThoraCAB group. The benefits previously reported with ThoraCAB in observational studies were not replicated in STET, but patients in the 2 groups had comparable quality of life at 12 months, and our data suggest that ThoraCAB is not obviously unsafe or inferior to OPCAB.

Limitations

The relatively small study size with only 3 surgeons participating represents a potential limitation. The study was powered to detect a 2-day difference in the primary outcome; it was not powered to detect the smaller difference observed, nor was it powered to detect differences in secondary outcomes. Only 1 OPCAB patient had a deep sternal wound infection, which was consistent with the reported 0.88% incidence rate,[22] so that one of the main proposed benefits of avoiding sternotomy was not evident. Such a benefit may be detected by a larger study or in a cohort at greater risk for sternal infection, but this was not supported by our data, which suggested a potentially greater difference in recovery time *in favor of OPCAB* for the patients with pre-existing diabetes. In addition, our results are unlikely to be altered substantially by a larger study because ThoraCAB had both advantages and disadvantages. Also, reductions in markers of the inflammatory response, a major determinant of postoperative outcome, were relatively small. The 18% reduction in IL-8 with ThoraCAB contrasts with an approximate 40% reduction observed in trials of OPCAB versus CABG with CPB,[18] where modest reductions in morbidity and resource use were evident.

The lack of masking was unavoidable but represents another limitation. To overcome this we adopted a definition of recovery based on objective criteria commonly used in making discharge decisions. A significant proportion of patients were discharged before all the criteria were met, and this was most prevalent in the ThoraCAB group, where the median postoperative hospital stay was shorter. This suggests either a possible bias on the part of attending clinicians or that the criteria used may not have adequately characterized clinicians' decisions. However, our conclusion that there was no difference in time to recovery or to discharge was supported by the majority of patients in both groups that believed the discharge decision was "about right."

The change to our definition of the primary end point part way through the trial is also a limitation. However, we do not believe that our imputation using time to hospital discharge for the Italian patients, for whom the additional data could not be retrieved retrospectively, biases our findings inasmuch as our conclusion was unchanged when these patients were excluded in a sensitivity analysis.

Resource Use

ThoraCAB patients were extubated earlier, an advantage observed to a greater extent in other series,[14] but this did not

TABLE 2. Secondary clinical outcomes

	Randomized to ThoraCAB (n = 91)		Randomized to OPCAB (n = 93)			*P*
	n	%	n	%	Effect (95% CI)	value
Length of hospital stay (d)*						
Median (IQR)	5 (5, 6)		6 (5, 7)		TR 0.94 (0.86, 1.02)	.16
Length of intensive care unit stay (h)						
Median (IQR)	22.4 (18.2, 25.2)		23.0 (19.5, 26.4)		HR 0.98 (0.73, 1.33)	.91
Intubation time (min)*						
Median (IQR)	256 (115, 464)		321 (194, 509)		TR 0.75 (0.60, 0.95)	.017
Death in hospital	1	1	0	0		
Participants' judgment about readiness for discharge†						
Too soon	1	1	1	1	OR 0.53 (0.22, 1.30)	.16
About right	69	82	64	76		
Could have been earlier	9	11	17	20		
Not sure	5	6	2	2		
Perioperative myocardial infarction‡	4	4	1	1		
Cardiac arrest§	0	0	0	0		
Hemodyamic support	40	44	36	39	OR 1.28 (0.67, 2.43)	.45
Arrhythmias§	21	23	32	35	OR 0.52 (0.26, 1.03)	.059
Pulmonary complications§	13	14	9	10	OR 1.56 (0.62, 3.90)	.34
Renal complications§	0	0	0	0		
Infective complications‖	10	11	10	11	OR 1.02 (0.40, 2.58)	.97
Gastrointestinal complications§	2	2	1	1		
Neurologic complications§	1	1	1	1		
Reoperation¶	4	4	0	0		
Blood loss in first 12 hours#						
GM	449		404		GMR 1.10 (0.97, 1.26)	.13
Total mediastinal fluid loss**						
GM	856		649		GMR 1.31 (1.15, 1.49)	<.001
Red blood cell transfusion after surgery††	7	8	12	13	OR 0.55 (0.20, 1.51)	.24
If yes, units transfused						
Median (IQR)	3 (1, 3)		2 (1, 3)			
Other transfusion after surgery‡‡	5	5	2	2		
Activated factor VII used after surgery?§§	0	0	0	0		
Asepsis score > 20 (any wound)						
Before discharge	0	0	1	1		
Six weeks after discharge‖‖	8	13	7	11	OR 1.16 (0.40, 3.41)	.78
Pain relief						
PCA duration (h)††						
Median (IQR)	38.8 (32.5, 47.2)		35.5 (24.8, 40.2)		TR 1.37 (1.25, 1.49)	<.0001
PCA volume (mg)§§§						
GM	50.9		48.2		GMR 1.04 (0.86, 1.24)	.69
Use of NSAIDs‡‡‡	16	18	9	10	OR 2.18 (0.89, 5.36)	.082
Use of tramadol§	57	66	45	49	OR 2.53 (1.11, 5.76)	.024
Use of codeine (or similar)‖‖	11	13	9	10	OR 1.28 (0.49, 3.36)	.61
Pain scores¶¶	(n = 84)		(n = 89)			
Two hours after extubation##						
Mean (SE)	35.0	2.50	35.0	2.52		
Twelve hours after extubation***						
Mean (SE)	30.1	1.76	30.2	1.78		
Twenty-four hours after extubation†††						
Mean (SE)	27.1	1.63	27.2	1.66		
Thirty-six hours after extubation‡‡‡‡						
Mean (SE)	25.1	1.56	25.1	1.59		

(Continued)

TABLE 2. Continued

	Randomized to ThoraCAB (n = 91)		Randomized to OPCAB (n = 93)			*P*
	n	%	n	%	Effect (95% CI)	value
Five days after extubation§§§§						
Mean (SE)	17.8	1.73	17.8	1.75		
Test for treatment time interaction						.67
Overall estimate of treatment effect					–0.063 (–3.85, 3.72)	.97

ThoraCAB, Off-pump coronary artery bypass surgery via a left anterolateral thoracotomy; *OPCAB,* off-pump coronary artery bypass surgery via a median sternotomy; *CI,* confidence interval; *IQR,* interquartile range; *TR,* time ratio; *HR,* hazard ratio; *OR,* odds ratio; *GM,* geometric mean; *GMR,* geometric mean ratio; *PCA,* patient-controlled analgesia; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *SE,* standard error. *One outlier was excluded (OPCAB group). †Comparison is ''could have been earlier'' versus ''too soon''/''about right.'' The most commonly occurring category (''about right'') was imputed for the 16 patients (7 ThoraCAB group, 9 OPCAB group) with missing data. The same treatment estimate and *P* value were obtained in a model without imputing missing data. ‡Defined as troponin I > 0.5 μg/L and at least 1 of the following: (1) new Qs in 2 contiguous leads, (2) new ST depression > 2 mm in 2 leads. One patient (OPCAB group) with missing data. §One patient (OPCAB group) with missing data. ||Adjustment for surgeon or center caused perfect prediction. Only diabetes and number of diseased vessels were adjusted for. ¶All reoperations occurred in the first 24 hours after surgery and were for bleeding. Two patients (OPCAB group) with missing data. #One outlier was excluded (ThoraCAB group). **One outlier was excluded (ThoraCAB group). Three patients (1 ThoraCAB group, 2 OPCAB group) with missing data. ††Two patients (OPCAB group) with missing data. ‡‡Other transfusions consist of the following: ThoraCAB group: platelets (n = 4), cryoprecipitate (n = 1); OPCAB group: fresh frozen plasma (n = 1), fresh frozen plasma and platelets (n = 1). Two patients (OPCAB group) with missing data. §§Two patients (ThoraCAB group) with missing data. ||||Data only collected for Bristol patients. Asepsis score ≤20 (most common category) was imputed for the 12 Bristol patients (6 ThoraCAB group, 6 OPCAB group) with missing data. ‡‡‡Five patients (3 ThoraCAB group, 2 OPCAB group) with missing data. §§§Five patients (4 ThoraCAB group, 1 OPCAB group) with missing data. |||Seven patients (4 ThoraCAB group, 3 OPCAB group) with missing data. ¶¶Thirteen patients had one score collected, 7 patients had two scores, 23 had three scores, 54 had four scores, and 74 had five scores. Method of pain assessment was missing for 25 observations (3.7%) on 19 individuals. The most common group (verbal) was imputed for these observations. ##Forty-six patients (19 ThoraCAB group, 27 OPCAB group) with missing data, including 25 patients recorded as asleep (10 ThoraCAB group, 15 OPCAB group). ***Twenty-eight patients (11 ThoraCAB group, 17 OPCAB group) with missing data, including 10 patients recorded as asleep (4 ThoraCAB group, 6 OPCAB group). †††Twenty-nine patients (9 ThoraCAB group, 20 OPCAB group) with missing data, including 7 patients recorded as asleep (3 ThoraCAB group, 4 OPCAB group). ‡‡‡‡Forty-six patients (19 ThoraCAB group, 27 OPCAB group) with missing data, including 12 patients recorded as asleep (6 ThoraCAB group, 6 OPCAB group). §§§§Estimates are provided at 5 days after extubation (approximate median time discharge score was done). Twenty-four patients (11 ThoraCAB group, 13 OPCAB group) with missing data. No patients were recorded as asleep.

translate into a benefit over OPCAB. This could be because (1) previous observational reports did not compare contemporaneous cohorts,[14-16] (2) the rapid discharge protocol advocated in these studies was not applicable to this cohort that was, on average, 10 years older,[14] (3) changing other clinicians' practice to extubate early was difficult and the average time to extubation was only reduced by approximately 1 hour, which is of limited clinical significance; and (4) patient transfer to less intensive levels of care was determined by institutional protocols that are influenced by postoperative organ dysfunction and nursing requirements.

Adequacy of Revascularization

A risk attendant to the use of MIDCAB techniques is that as invasiveness declines so too does the completeness of revascularization. Fewer grafts were performed in the ThoraCAB group despite the 2 groups being well matched in the

TABLE 3. Pulmonary function

	Randomized to ThoraCAB (n = 63)		Randomized to OPCAB (n = 64)		Mean difference (ThoraCAB-OPCAB) (95% CI)	*P* value
Baseline	Mean	SD	Mean	SD		
FEV_1 (L)*	2.84	0.69	2.48	0.73		
FVC (L)†	3.56	0.76	3.22	0.88		
PEF (L/m)‡	379	135	371	140		
FEV_1/FVC ratio (%)§	78.9		76.2			
Discharge	Mean	SE	Mean	SE		
FEV_1 (L)||	1.48	0.10	1.61	0.09	–0.13 (–0.28, 0.02)	.09
FVC (L)||	1.90	0.11	2.15	0.11	–0.25 (–0.44, –0.06)	.01
PEF (L/m)||	229	21	255	21	–26 (–62, 11)	.17
FEV_1/FVC ratio (%)¶	78.8		77.7		1.01 (0.96, 1.07)	.58

ThoraCAB, Off-pump coronary artery bypass surgery via a left anterolateral thoracotomy; *OPCAB,* off-pump coronary artery bypass surgery via a median sternotomy; *CI,* confidence interval; *SD,* standard deviation; *FEV_1,* forced expiratory volume in 1 second; *FVC,* forced vital capacity; *SE,* standard error; *PEF,* peak expiratory flow. *Nine patients (3 ThoraCAB group, 6 OPCAB group) with missing data. †Ten patients (four ThoraCAB group, six OPCAB group) with missing data. ‡Eleven patients (4 ThoraCAB group, 7 OPCAB group) with missing data. §Results are presented as geometric means as the analysis was performed on the log scale. Ten patients (4 ThoraCAB group, 6 OPCAB group) with missing data. ||Forty patients (24 ThoraCAB group, 16 OPCAB group) with missing data. ¶Results are presented as geometric means and geometric mean ratios (ThoraCAB/OPCAB) as the analysis was performed on the log scale. Forty patients (24 ThoraCAB group, 16 OPCAB group) with missing data. Eight (1 ThoraCAB, 7 OPCAB) outlying observations on 6 individuals were excluded from this analysis (4 observations at baseline and 4 observations at discharge), resulting in 2 patients (both in the OPCAB group) being excluded from this analysis.

extent and severity of their coronary disease. This may reflect a learning curve with ThoraCAB. The STET surgeons had all performed more than 30 ThoraCAB procedures before joining the trial and had extensive experience with MICS,[3,9] but nonetheless their experience with ThoraCAB was significantly less than with OPCAB (>200 procedures). Also, ThoraCAB, unlike OPCAB, was not available outside the trial.

CONCLUSIONS

This is the first RCT of ThoraCAB versus OPCAB. We have demonstrated that the benefits of ThoraCAB—reduced inflammatory response, shorter intubation times, and fewer arrhythmias—are offset by longer operations with fewer grafts, a greater need for postoperative pain relief, worse lung function at discharge, and higher costs. We have also shown that the patients' quality of life at 12 months is similar with the 2 procedures. Our results are at odds with the benefits reported in observational studies; our experience with ThoraCAB is less than with OPCAB and further evaluation is needed before widespread dissemination.

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APPENDIX E1

Primary Outcome—Component Definitions

Infection was defined as (a) systemic lower respiratory tract infection, comprising (i) systemic inflammatory response syndrome (SIRS) *and* (ii) antibiotic treatment for suspected or proven infection *and* (iii) at least one of productive cough, new or progressive infiltrates on chest radiograph, positive sputum culture or declining oxygenation **or** (b) wound infection defined as an in-hospital ASEPSIS score greater than 20 (each wound assessed separately)[19] **or** (c) sepsis that comprised (i) documented culture-positive infection or intravenous antibiotic treatment for suspected infection *and* (ii) SIRS.

SIRS was defined as 2 or more of the following: (i) temperature >38°C or <36°C; (ii) heart rate >90 beats/minute; (iii) respiratory rate <20 breaths/min or arterial carbon dioxide tension <32 mm Hg; (iv) white blood cell count >12,000/mm^3 or <4000/mm^3

Normal routine blood test results and temperature were defined as (a) white blood cell count ≥4000/mm^3 and ≤12,000/mm^3 and (b) temperature ≥36°C and ≤38°C.

Physical fitness was defined as the ability to walk 70 m, having an oxygen saturation on air ≥95%, and having had the bowels opened.

Cost Analysis

National Health Service reference costs for 2008/2009 were used.[23] Operative and ward costs were not available for 2008/2009, so costs from earlier years[24,25] inflated to 2008/2009 levels using pay and prices index figures[26] were used.

Statistical Methods

For the comparison of pain scores between the OPCAB and ThoraCAB groups, the analysis was adjusted for factors included in the cohort minimization plus the assessment method (visual analog scale or verbal). Also, for the analysis of biomarkers, interactions of surgeon, diabetes, and number of diseased vessels with time were considered.

Time-to-event outcomes were compared using hazard ratios or time ratios (TR), depending on the model used. The model (Cox proportional hazards or parametric accelerated failure time) was chosen on the basis of the validity of the model assumptions and goodness of fit, assessed graphically and using the Akaike information criterion.[27] Time-to-event curves were constructed using the Kaplan-Meier method. Continuous outcomes were compared using a difference in means, with logarithmic transformations if distributions were skewed. For transformed data, the results were transformed back to the original scale after analysis and the results presented as geometric means, with the treatment difference expressed as a ratio of geometric means. Binary outcomes were compared using odds ratios. Formal statistical comparisons are presented for binary outcomes only if more than 10 patients experienced the outcome (with at least 1 event in each treatment group). For multicategory outcomes, ordinal or multinomial logistic regression was used as appropriate. Categories were combined if fewer than 5% of patients were in any 1 category across both treatment groups. Repeated measures of continuous outcomes were analyzed using the linear mixed effects methodology, and where the outcome was measured both preoperatively and postoperatively, the preoperative and postoperative values were modeled jointly to avoid the need to exclude or impute values for cases with missing preoperative values. Treatment-by-time interactions were examined where possible, and if the interaction was statistically significant at the 10% level using a likelihood ratio test, changes in treatment effect with time are described; otherwise, an overall treatment effect is reported.

Missing data in baseline characteristics are indicated by footnotes and did not differ substantially between groups. Missing data for outcomes compared at a single time point were infrequent (<5%); for these outcomes, the analyses presented use cases with complete data. The only exceptions to this were the patients' judgment of readiness for discharge and 6-week wound infection (both 9% missing data), where imputation of the most common categories was used. For longitudinal outcomes, missing data was more common (eg, 25% of pain scores are missing). For these analyses, variables predictive of missingness were identified and included in the model.

Statistical tests for baseline imbalance were not carried out inasmuch as such hypothesis testing can be misleading.[28]

Mixed models were fitted in SAS version 9.2 (SAS Institute Inc, Cary, NC) and MLwin version 2.1 (Centre for Multilevel Modelling, University of Bristol, United Kingdom). All other analyses were performed using Stata version 11.1 (StataCorp LP, College Station, Tex).

Interim Analysis

The Data Monitoring and Safety Committee periodically reviewed the safety data and a formal interim analysis of time until fit for discharge, total postoperative hospital stay, and pain scores, which was performed when 50% of patients had been recruited. The *P* values reported are not corrected for this interim analysis.

Reasons for Not Receiving the Allocated Treatment

Patient request (2, one in each group), poor gas exchange (1), severe vascular disease (1), high-risk patient (3), poor left ventricular function (1), and ascending aortic aneurysm (1).

Reasons for conversion to on-pump surgery were hemodynamic instability/ST elevation (6), unknown hemorrhagic

pericarditis (1), intramyocardial vessels (1), severe coronary calcification (1), ventricular fibrillation before grafting (1), and not recorded (1).

Sensitivity Analyses of Time Until Fit for Discharge

Five sensitivity analyses were undertaken:

1. Test for different treatment effects at the 2 centers ($P = .71$)
2. Excluding protocol violations (TR, 1.04; 95% CI, 0.94, 1.15; $P = .48$)
3. Excluding patients without mobility-related fitness data (TR, 1.01; 95% CI, 0.91, 1.12; $P = .85$)
4. Relaxing the assumption of a common baseline hazard for all patients, through stratification by center (TR, 1.03; 95% CI, 0.94, 1.14; $P = .51$)
5. Assessing the impact of possible informative censoring by (i) assuming fitness was observed for all patients (TR, 0.99; 95% CI, 0.91, 1.08; $P = .82$) and (ii) assuming all censored times had the longest observed time to fitness (TR, 1.01; 95% CI, 0.92, 1.12; $P = .78$).

TABLE E1. Expected adverse events by treatment received: Patients who had off-pump surgery

	Surgery via ThoraCAB (n = 84)		Surgery via OPCAB (n = 89)		Overall (n = 173)	
	n	%	n	%	n	%
PATIENTS WITH 1 OR MORE EXPECTED EVENT	**70**	**83**	**77**	**87**	**147**	**85**
PREDISCHARGE EVENTS						
Perioperative MI*	**11**	**13**	**2**	**2**	**13**	**8**
New Qs in 2 contiguous leads*	0	0	0	0	0	0
Raised troponin I (>0.5 μg/L)*	11	13	2	2	13	8
New ST depression > 2 mm in 2 leads*	3	4	1	1	4	2
Cardiac arrest*	**0**	**0**	**0**	**0**	**0**	**0**
Hemodynamic support	**34**	**40**	**39**	**44**	**73**	**42**
Any inotropes (excluding norepinephrine)*	6	7	1	4	7	4
Norepinephrine used*	17	20	22	25	39	23
IABP*	0	0	1	1	1	1
Pulmonary artery catheter*	0	0	0	0	0	0
Vasodilator	17	20	17	19	34	20
Arrhythmias*	**17**	**20**	**31**	**35**	**48**	**28**
SVT/AF requiring treatment*	16	19	30	34	46	27
VF/VT requiring intervention*	2	2	2	2	4	2
Pacing†	0	0	3	3	3	2
Pulmonary complications*	**11**	**13**	**11**	**13**	**22**	**13**
Reintubation and ventilation*	3	4	3	3	6	3
Tracheostomy*	2	2	0	0	2	1
Mask CPAP*	10	12	10	11	20	12
ARDS*	0	0	0	0	0	0
Renal complications* (new hemofiltration/dialysis)	**0**	**0**	**0**	**0**	**0**	**0**
Infective complications	**67**	**80**	**76**	**85**	**143**	**83**
Septicemia*	1	1	1	1	2	1
Culture-positive sputum*	0	0	2	2	2	1
Productive cough‡	38	45	37	43	75	44
Temperature >38°C or <36°C	9	11	12	13	21	12
White cell count >12,000 or <4000	46	55	53	60	99	57
Raised CRP (>100)	58	69	68	76	126	73
New/progressive radiographic infiltrates on chest x-ray film	11	13	9	10	20	12
Heart rate >90 beats/min*	47	56	52	59	99	58
Respiratory rate >20 breaths/min or $Paco_2$ <32 mm Hg	49	58	51	57	100	58
IV antibiotics*	6	7	12	14	18	10
Oral antibiotics*	8	10	8	9	16	9
GI complications*	**2**	**2**	**1**	**1**	**3**	**2**
Peptic ulcer/GI bleed/perforation*	1	1	1	1	2	1
Pancreatitis*	0	0	0	0	0	0
Other (eg, laparotomy, obstruction)*	1	1	0	0	1	1
Neurologic complications*	**1**	**1**	**1**	**1**	**2**	**1**
Stroke*	0	0	0	0	0	0
Coma or confusion state*	1	1	1	1	2	1
TIA*	0	0	0	0	0	0
Reoperation§	**3**	**4**	**1**	**1**	**4**	**2**
Death before discharge	**1**	**1**	**0**	**0**	**1**	**1**
POSTDISCHARGE EVENTS						
Possibly related	**2**	**2**	**1**	**1**	**3**	**2**
Stroke resulting in readmission and subsequent death	0		1		1	
Readmission with ventricular tachycardia; ICD inserted						
Further readmissions with ICD problems and arrhythmias	1		0		1	
Wound infection requiring readmission	1		0		1	

(Continued)

TABLE E1. Continued

	Surgery via ThoraCAB (n = 84)		Surgery via OPCAB (n = 89)		Overall (n = 173)	
	n	%	n	%	n	%
Probably related	**1**	**1**	**0**	**0**	**1**	**1**
Wound infection requiring readmission	1		0		1	
Unrelated	**0**	**0**	**3**	**3**	**3**	**2**
Chest infection/pneumonia requiring readmission						
Respiratory failure resulting in death	0		1		1	
Readmitted for drainage of large left pleural effusion						
Discharged home after 5 d after removal of drain	0		1		1	
Repeat admissions to A&E with pericardial effusion and left pleural effusion						
Undergoing follow-up outpatient appointments with cardiologist	0		1		1	
Relationship unknown	**2**	**2**	**5**	**6**	**7**	**4**
Leg infection	0		1		1	
Septic leg	1		0		1	
Arrhythmia	1		0		1	
Pleural effusion	0		1		1	
TIA	0		1		1	
Wound infection||	0		1		1	
Sternum infection/not healing	0		1		1	

Each bold event is composed of the events listed below it. A patient can experience more than 1 of the component events. *ThoraCAB,* Off-pump coronary artery bypass surgery via a left anterolateral thoracotomy; *OPCAB,* off-pump coronary artery bypass surgery via a median sternotomy; *MI,* myocardial infarction; *IABP,* intra-aortic balloon pump; *SVT,* supraventricular tachycardia; *AF,* atrial fibrillation; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia; *CPAP,* continuous positive airway pressure; *ARDS,* acute respiratory distress syndrome; *CRP,* C-reactive protein; *$Paco_2$*, arterial carbon dioxide tension; *IV,* intravenous; *GI,* gastrointestinal; *TIA,* transient ischemic attack; *ICD,* implantable cardioverter defibrillator; A&E, accident and emergency. *One patient (OPCAB group) with missing data. †Pacing was permanent for 1 patient in the OPCAB group (status unknown for the remaining 2 patients). One patient (OPCAB group) with missing data. ‡Two patients (both OPCAB group) with missing data. §All reoperations occurred in the first 24 hours after surgery and were for bleeding. Two patients (both OPCAB group) with missing data. ||Patient admitted twice for this reason.

TABLE E2. Expected adverse events by treatment received: Patients who had on-pump surgery

	Surgery via ThoraCAB (n = 0)		Surgery via OPCAB (n = 11)	
	n	%	n	%
PATIENTS WITH 1 OR MORE EXPECTED EVENT			**7**	**64**
PREDISCHARGE EVENTS				
Perioperative MI			**2**	**18**
New Qs in 2 contiguous leads			1	
Raised troponin I (>0.5 μg/L)			2	
New ST depression >2 mm in 2 leads			0	
Cardiac arrest			**0**	**0**
Hemodynamic support			**3**	**27**
Any inotropes (excluding norepinephrine)			3	
Norepinephrine used			2	
IABP			1	
Pulmonary artery catheter			1	
Vasodilator			0	
Arrhythmias			**5**	**45**
SVT/AF requiring treatment			5	
VF/VT requiring intervention			1	
Pacing			0	
Pulmonary complications			**0**	**0**
Reintubation and ventilation			0	
Tracheostomy			0	
Mask CPAP			0	
ARDS			0	
Renal complications (new hemofiltration/dialysis)			**0**	**0**
Infective complications			**6**	**55**
Septicemia			1	
Culture-positive sputum			0	
Productive cough			0	
Temperature >38°C or <36°C			1	
White cell count >12,000 or <4,000			6	
Raised CRP (>100)			2	
New/progressive radiographic infiltrates on chest radiograph			0	
Heart rate >90 beats/min			2	
Respiratory rate >20 breaths/min or $Paco_2$ <32 mm Hg			2	
IV antibiotics			1	
Oral antibiotics			0	
GI complications			**0**	**0**
Peptic ulcer/GI bleed/perforation			0	
Pancreatitis			0	
Other (eg, laparotomy, obstruction)			0	
Neurologic complications			**0**	**0**
Stroke			0	
Coma or confusion state			0	
TIA			0	
Reoperation			**0**	**0**
Death before discharge			**0**	**0**
POSTDISCHARGE EVENTS				
Relationship unknown			**1**	**0**
Pleural effusion, suspected heart attack			1	

Each bold event is composed of the events listed below it. A patient can experience more than 1 of the component events. *ThoraCAB,* Off-pump coronary artery bypass surgery via a left anterolateral thoracotomy; *OPCAB,* off-pump coronary artery bypass surgery via a median sternotomy; *MI,* myocardial infarction; *IABP,* intra-aortic balloon pump; *SVT,* supraventricular tachycardia; *AF,* atrial fibrillation; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia; *CPAP,* continuous positive airway pressure; *ARDS,* acute respiratory distress syndrome; *CRP,* C-reactive protein; *$Paco_2$*, arterial carbon dioxide tension; *IV,* intravenous; *GI,* gastrointestinal; *TIA,* transient ischemic attack; *ICD,* implantable cardioverter defibrillator; *A&E,* accident and emergency.

TABLE E3. Unexpected adverse events by treatment received

Patients who had off-pump surgery*	Surgery via ThoraCAB (n = 84)	Surgery via OPCAB (n = 89)	Overall (n = 173)
Patients with 1 or more unexpected event	10 (12%)	7 (8%)	17 (10%)
Definitely related	1	0	1
Left heart hernia through thoracotomy wound requiring readmission			
Ventricular hernia repair via thoracotomy and sternotomy	1	0	1
Probably related	**1**	**0**	**1**
Hemothorax requiring readmission, clot and type A aortic dissection, bilateral effusions, h ematoma in right ventricle, renal failure	1	0	1
Unlikely to be related	**1**	**0**	**1**
Readmission for chest pain and shortness of breath. Investigations could not find likely cause. Discharged after 26 d after prescription of anxiety drugs	1	0	1
Unrelated	**3**	**0**	**3**
Readmitted for lead replacement to ICD	1	0	1
Readmission owing to pain at ICD site	1	0	1
Delayed reaction to antibiotics causing rash and pyrexia	1	0	1
Relationship unknown	**4**	**7**	**11**
Chest pain—not cardiac	1	0	1
Hernia	0	1	1
Pleurisy	0	1	1
Sternum—wiring/clip problems	0	1	1
Chest pain	1	0	1
ECG, 24 h	0	1	1
Shortness of breath, chest radiographs†	1	0	1
Pneumonia	1	0	1
Chest pain, blood pressure monitor for 24 h†	0	1	1
Thrombosis/embolism	0	1	1
Irregular heartbeat	0	1	1

ThoraCAB, Off-pump coronary artery bypass surgery via a left anterolateral thoracotomy; *OPCAB,* off-pump coronary artery bypass surgery via a median sternotomy; *ICD,* implantable cardioverter defibrillator; *ECG,* electrocardiogram. *There were no events in patients who had on-pump surgery (n = 11). †Each of these patients was admitted twice for the same reason.

TABLE E4. Pain relief —additional information (ThoraCAB patients only)

	Randomized to ThoraCAB (n = 91)	
	n	%
PV block volume in first 24 h		
Median (IQR) mL	234 (90, 250)	
PV block volume overall		
Median (IQR) mL	360 (95, 520)	
PV block complications		
Cardiac arrest*	0	0
Convulsions without cardiac arrest*	1	1
Persistent hypotension*	1	1
PV block failure†	9	11

ThoraCAB, Off-pump coronary artery bypass surgery via a left anterolateral thoracotomy; *PV,* paravertebral; *IQR,* interquartile range. *Twenty-two patients with missing data. †Of the patients with PV block failure, 6 had at least one bolus, 1 had an intercostal block, 4 had nurse-administered intravenous morphine, and none had diclofenac, intravenous ketamine, clonidine, or any other pain relief. Eleven patients have missing data.

TABLE E5. Biochemical inflammatory markers

Variable (log-scale)	Randomized to ThoraCAB (n = 30)		Randomized to OPCAB (n = 27)		Mean difference (ThoraCAB-OPCAB) (95% CI)	GMR (95% CI)	*P* value
Baseline	Mean	SD	Mean	SD			
IL-6 (pg/mL)*	1.17	0.64	1.35	0.93			
IL-8 (pg/mL)†	1.96	0.51	2.01	0.46			
IL-10 (pg/mL)‡	2.14	0.52	2.10	0.49			
C3a (ng/mL)§	7.74	0.30	7.52	0.50			
C5a (ng/mL)‖	2.76	0.40	2.62	0.42			
After intervention	Mean	SE	Mean	SE			
IL-6 (pg/mL)	(n = 29)		(n = 27)				
End of surgery¶	5.29	0.24	5.10	0.25	0.19 (–0.22,0.59)	1.21 (0.80, 1.80)	
Four hours after surgery#	5.66	0.19	6.00	0.19	–0.33 (–0.64, –0.01)	0.72 (0.53, 0.99)	
Twelve hours after surgery**	5.79	0.25	5.85	0.25	–0.06 (–0.49, 0.38)	0.94 (0.61, 1.46)	
Twenty-four hours after surgery††	5.80	0.22	5.84	0.22	–0.04 (–0.41,0.33)	0.96 (0.66, 1.39)	
Test for treatment time interaction							.013
IL-8 (pg/mL)	(n = 29)		(n = 27)				
End of surgery**	2.91	0.17	3.08	0.17			
Four hours after surgery‡‡	3.34	0.15	3.52	0.15			
Twelve hours after surgery**	3.61	0.17	3.62	0.17			
Twenty-four hours after surgery#	3.37	0.17	3.64	0.17			
Test for treatment time interaction							.12
Overall estimate of treatment effect					–0.19 (–0.38, –0.004)	0.82 (0.68, 0.99)	.044
IL-10 (pg/mL)	(n = 26)		(n = 25)				
End of surgery**	2.66	0.27	2.34	0.28			
Four hours after surgery‡‡	2.86	0.23	2.72	0.24			
Twelve hours after surgery**	2.97	0.22	3.09	0.23			
Twenty-four hours after surgery#	2.98	0.26	3.07	0.27			
Test for treatment time interaction							.23
Overall estimate of treatment effect					0.04 (–0.22, 0.30)	1.04 (0.80, 1.35)	.77
C3a (ng/mL)	(n = 30)		(n = 27)				
End of surgery**	7.74	0.12	7.61	0.13	0.13 (–0.08,0.33)	1.14 (0.92, 1.39)	
Four hours after surgery‡‡	7.52	0.12	7.41	0.12	0.11 (–0.10,0.31)	1.12 (0.90, 1.36)	
Twelve hours after surgery**	7.40	0.12	7.56	0.12	–0.17 (–0.35,0.01)	0.84 (0.70, 1.01)	
Twenty-four hours after surgery‖	7.62	0.13	7.75	0.13	–0.13 (–0.34,0.08)	0.87 (0.71, 1.08)	
Test for treatment ·time interaction							.007
C5a (ng/mL)	(n = 30)		(n = 27)				
End of surgery‖	2.64	0.12	2.58	0.13			
Four hours after surgery	2.85	0.11	2.73	0.12			
Twelve hours after surgery	2.90	0.12	2.81	0.12			
Twenty-four hours after surgery	3.10	0.13	3.02	0.13			
Test for treatment ·time interaction							.70
Overall estimate of treatment effect					0.09 (–0.03, 0.20)	1.09 (0.97, 1.22)	.12

ThoraCAB, Off-pump coronary artery bypass surgery via a left anterolateral thoracotomy; *OPCAB,* off-pump coronary artery bypass surgery via a median sternotomy; *GMR,* geometric mean ratio; *CI,* confidence interval; *SD,* standard deviation; *IL,* interleukin; *C,* complement. *Six patients (2 ThoraCAB group, 4 OPCAB group) with missing data. †Six patients (1 ThoraCAB group, 5 OPCAB group) with missing data. ‡Eleven patients (5 ThoraCAB group, 6 OPCAB group) with missing data. §Seven patients (1 ThoraCAB group, 6 OPCAB group) with missing data. ‖One patient (OPCAB group) with missing data. ¶Three patients (OPCAB group) with missing data. #Two patients (1 ThoraCAB group, 1 OPCAB group) with missing data. **Two patients (OPCAB group) with missing data. ††Two patients (ThoraCAB group) with missing data. ‡‡Three patients (2 ThoraCAB group, 1 OPCAB group) with missing data.

TABLE E6. Hospital resource use and costs

	Randomized to ThoraCAB (n = 91): GM	Randomized to OPCAB (n = 93): GM	Effect (95% CI)	*P* value
Total cost*	£5079	£4566	GMR 1.10 (1.02, 1.18)	.007
Operation cost	£2363	£1987		
Reoperation cost†	£869	£0		
Intensive care unit cost	£1411	£1430		
High dependency unit cost	£831	£613		
Ward cost	£293	£381		
Readmission cost‡	£888	£428		

ThoraCAB, Off-pump coronary artery bypass surgery via a left anterolateral thoracotomy; *OPCAB,* off-pump coronary artery bypass surgery via a median sternotomy; *CI,* confidence interval; *GM,* geometric mean; *GMR,* geometric mean ratio. *Three outliers were excluded from model (2 ThoraCAB group, 1 OPCAB group). †Four patients had a reoperation (all ThoraCAB group). ‡Twenty three patients were readmitted in the first postoperative year (10 ThoraCAB group, 13 OPCAB group).

TABLE E7. Quality of life scores (Coronary Revascularization Outcome Questionnaire)

	Randomized to ThoraCAB (n = 66)			Randomized to OPCAB (n = 66)			Effect (95% CI)	*P* value
Baseline	n	Mean	SD	n	Mean	SD		
Core total	62	49.7	6.12	63	50.2	6.73		
Symptoms	63	74.5	19.6	63	73.8	21.7		
Physical functioning	62	72.9	26.1	63	69.0	28.3		
Psychosocial functioning	62	65.7	21.8	63	70.0	23.9		
Cognitive functioning	62	79.5	23.0	63	82.9	25.2		
Follow-up	n	Mean	SE		Mean	SE		
Core total*								
Three months	53	48.3	1.13	50	48.9	1.17		
Twelve months	56	48.7	1.14	54	49.1	1.18		
Test for treatment time interaction								.81
Overall estimate of treatment effect							–0.47 (–1.94, 0.99)	.52
Symptoms†								
Three months	53	91.5	1.83	50	92.1	1.93		
Twelve months	56	95.0	1.48	54	96.9	1.63		
Test for treatment time interaction								.51
Overall estimate of treatment effect							–1.64 (–3.88, 0.59)	.15
Physical functioning‡								
Three months	53	84.6	3.96	50	87.3	4.17		
Twelve months	55	94.5	3.65	54	91.6	3.89		
Test for treatment time interaction								.12
Overall estimate of treatment effect							1.26 (–3.98, 6.51)	.63
Psychosocial functioning§								
Three months	53	74.0	3.18	50	74.7	3.30		
Twelve months	56	84.8	2.58	54	85.7	2.81		
Test for treatment time interaction								.95
Overall estimate of treatment effect							–0.83 (–4.63, 2.97)	.66
Cognitive functioning‖								
Three months	53	81.7	3.43	50	81.6	3.59		
Twelve months	54	87.9	2.93	54	89.2	3.19		
Test for treatment time interaction								.67
Overall estimate of treatment effect							–0.96 (–5.25, 3.32)	.65
Satisfaction¶								
Three months	51	81.6	3.05	50	82.9	3.32		
Twelve months	55	82.7	3.07	54	87.7	3.38		
Test for treatment time interaction								.15
Overall estimate of treatment effect							–3.21 (–8.19, 1.77)	.20
Adverse events#								
Three months	51	80.4	2.37	50	81.5	2.58		
Twelve months	55	89.4	2.40	54	88.7	2.62		
Test for treatment time interaction								.40
Overall estimate of treatment effect							–0.17 (–4.01, 3.67)	.93

The number of observations varies slightly between different scores owing to insufficient data being available to calculate scores for a small number of observations. *ThoraCAB,* Off-pump coronary artery bypass surgery via a left anterolateral thoracotomy; *OPCAB,* off-pump coronary artery bypass surgery via a median sternotomy; *CI,* confidence interval; *SD,* standard deviation; *SE,* standard error. *Three outliers were excluded for 12-month scores (1 in ThoraCAB group, 2 in OPCAB group). A compound symmetry covariance pattern was used. †One outlier was excluded for 3-month scores (ThoraCAB group); 4 outliers were excluded for 12-month scores (1 in ThoraCAB group, 3 in OPCAB group). A general (unstructured) covariance pattern was used. ‡No outliers were excluded. A general (unstructured) covariance pattern was used. §Two outliers were excluded for 12-month scores (1 in ThoraCAB group, 1 in OPCAB group). A general (unstructured) covariance pattern was used. ||Two outliers were excluded for 12-month scores (both in ThoraCAB group). A general (unstructured) covariance pattern was used. ¶Two outliers were excluded for 3-month scores (both in ThoraCAB group); 4 outliers were excluded for 12-month scores (2 in ThoraCAB group, 2 in OPCAB group). A compound symmetry covariance pattern was used. #Two outliers were excluded for 12-month scores (both in ThoraCAB group). A compound symmetry covariance pattern was used.