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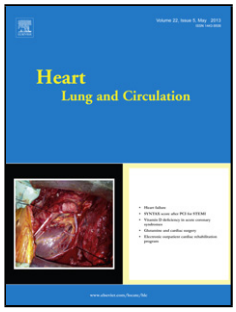

Title: Extracorporeal Membrane Oxygenation for Very High-risk Transcatheter Aortic Valve Implantation

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PII: S1443-9506(14)00462-4
DOI: http://dx.doi.org/doi:10.1016/j.hlc.2014.05.006
Reference: HLC 1600

To appear in:

Received date: 22-3-2014
Revised date: 1-5-2014
Accepted date: 8-5-2014

Please cite this article as: Seco M, Forrest P, Jackson SA, Martinez G, Andvik S, Bannon PG, Ng M, Fraser J, Wilson MK, Vallely MP, Extracorporeal Membrane Oxygenation for Very High-risk Transcatheter Aortic Valve Implantation, *Heart, Lung & Circulation* (2014), http://dx.doi.org/10.1016/j.hlc.2014.05.006

Abstract

Background: Transcatheter aortic valve implantation (TAVI) can cause profound haemodynamic perturbation in the peri-operative period. Veno-arterial extracorporeal membrane oxygenation (ECMO) can be used to provide cardiorespiratory support during this time, either prophylactically or emergently.

Method: 100 TAVI procedures were performed between 2009 and 2013 in our institution. ECMO was used in 11 patients, including eight prophylactic and three rescue cases. Rescue ECMO was required for ventricular fibrillation after valvuloplasty, and aortic annulus rupture. The criteria for prophylactic ECMO included heart failure requiring stabilisation pre-TAVI, haemodynamic instability with balloon aortic valvuloplasty performed to improve heart function pre-TAVI, moderate or severe left and/or right ventricular failure, or borderline haemodynamics at procedure. Differences in preoperative characteristics and postoperative outcomes between ECMO and non-ECMO TAVI patients were compared, and significant results were further assessed controlling for EuroSCORE.

Results: Compared to TAVI patients who did not require ECMO, ECMO patients had significantly ($p<.05$) higher mean EuroSCORE (51 vs. 30%). Postoperative outcomes, however, were largely comparable between the two groups. All-cause mortality occurred in nil prophylactic ECMO patients, one rescue ECMO patient, and two non-ECMO patients. The difference in mortality between ECMO and non-ECMO patients was not significantly different (9 vs. 2%; $p>.05$). ECMO patients were more likely to develop acute renal failure than non-ECMO patients (36 vs. 8%, $p<.05$), which was most likely due to haemodynamic collapse and end-organ dysfunction in patients that required ECMO rescue.

Conclusions: Instituting prophylactic ECMO in selected very high-risk patients may help avoid consequences of intraoperative complications and the need for emergent rescue ECMO.

Keywords: Extracorporeal membrane oxygenation; Heart valve, percutaneous; Aortic valve, replacement; Cardiac shock

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Running Head: ECMO for very high-risk TAVI

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Word Count (excluding abstract): 4188

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Introduction

Transcatheter aortic valve implantation (TAVI) has been shown to be an effective method of treating severe aortic stenosis in patients who are deemed too high-risk for surgical aortic valve replacement [1]. Consequently TAVI patients generally have multiple comorbidities including coronary artery disease, peripheral vascular disease, renal insufficiency, and severely impaired ventricular function.

Veno-arterial (VA) extracorporeal membrane oxygenation (ECMO) can provide temporary cardiorespiratory support by performing the vital functions of haemodynamic support and oxygenation. It can be used in both an elective setting to provide prophylactic intraoperative support, or in emergent settings as rescue for low cardiac output. During the early phase of our institution's TAVI program we have used both prophylactic and rescue ECMO during TAVI procedures in very high-risk patients. The aim of this study was to analyse the outcomes of these patients, and to determine whether prophylactic ECMO support can improve outcomes.

Methods

Data for TAVI patients at our institution (The Royal Prince Alfred Hospital, Sydney) was prospectively collected. A case-controlled study of all patients that received TAVI procedures, with and without the use of ECMO, was performed. Approval for the study was granted by the Sydney Local Health District Ethics Review Committee (RPAH zone). VA ECMO was classified into either: prophylactic ECMO, where usage was planned prior to the procedure; or rescue ECMO, where ECMO was emergently instituted for rescue from intraoperative complications. Other endpoints were defined using the updated Valve Academic Research Consortium Guidelines (VARC2) [2].

Patients

Between June 2009 and June 2013, 100 TAVI procedures were performed: 68 by a transfemoral approach, and 32 by a transapical (TA) approach [3]. The first nine patients received an Edward SAPIEN (ES) valve, then 89 patients received an ES-XT valve and two patients received a Medtronic

CoreValve. VA ECMO was used in a total of 11 (11%) patients, which included four TF patients (5.9% of all TF patients) and seven TA patients (21.9% of all TA patients). Of these 11 ECMO patients, eight (72.7%) received prophylactic ECMO and three (27.3%) required rescue ECMO. The reasons for using rescue ECMO in three patients were: two patients developed ventricular fibrillation (VF) after valvuloplasty resulting in cardiogenic shock that could not be promptly cardioverted; and one experienced an aortic annulus rupture and tamponade causing rapid haemodynamic collapse (the management and outcome of this patient has been previously reported in detail [4]). The decision to use prophylactic ECMO in 11 patients was made between the cardiothoracic surgeon, cardiologist, and anaesthetist. The criteria included a combination of:

1. Heart failure requiring hospitalisation and stabilisation pre-TAVI
2. Pre-operative assessment of moderate or severe left and/or right ventricular failure
3. Haemodynamic instability during BAV performed to improve heart function pre-TAVI
4. Borderline haemodynamics at procedure with central venous pressure/pulmonary capillary wedge pressure >20mmHg, mean pulmonary artery pressure >40mmHg, and cardiac index <2.0 with no improvement on inotropes.

Operative Method

TAVI at our institution is performed by a 'Heart Team', which is a joint approach between cardiologists, cardiac surgeons, anesthetists, perfusionists, and others [5]. The method used to perform transfemoral and transapical TAVI with an ES valve has been described [6]. A transfemoral-first approach to TAVI was used. If transfemoral access was contraindicated due to small, atherosclerotic or tortuous iliofemoral or aortic vessels then transapical access was used. VA ECMO was established percutaneously via cannulation of the femoral or jugular vein for outflow and axillary or femoral arteries for inflow. The ECMO circuit consisted of Jostra Rotaflow (Jostra AG, Hirrlingen, Germany) centrifugal pump with a Quadrox D oxygenator. After cannulation the circuit was primed with crystalloid solution, anticoagulation achieved with heparin, and extracorporeal blood flow was established. Flows were initiated at 60-100cc/kg/min and increased if required.

Statistical Analysis

Statistical analysis was performed with R (R Core Team, Vienna, Austria). The difference in baseline characteristics and postoperative outcomes between patients receiving any or no ECMO, and prophylactic or rescue ECMO were tested. Differences in the means of continuous variables were tested via the use of an independent samples *t*-test, while proportional differences in categorical variables were tested via the use of a Chi-square (χ^2) test of independence. Significant mean differences in perioperative outcomes were additionally submitted to logistic regression to investigate whether differences were predicted by ECMO status (any or none), while controlling for preoperative surgical risk, represented by EuroSCORE.

Results

Baseline Patient Characteristics

Baseline patient characteristics and the difference between ECMO and non-EMCO patients are presented in Table 1. EuroSCORE was significantly higher for ECMO than non-ECMO patients (51.7 ± 24.9% vs. 30.8 ± 21.3%, $p<.05$). ECMO patients had significantly higher mean pulmonary artery pressure (39.4 ± 10.7mmHg vs. 30.4 ± 9.2mmHg, $p<.05$), were more likely to have pulmonary artery systolic pressure ≥ 60mmHg (67% vs. 20%, $p<.01$), and were more likely to have right ventricular dysfunction (either mild, moderate or severe) (55% vs. 3%, $p<.01$). These differences were expected, as they were used as primary indications for ECMO support. ECMO patients also had lower mean and peak transaortic gradients (39.7 ± 7.7mmHg vs. 46.0 ± 12.5mmHg, $p<.05$; and 59.8 ± 14.1mmHg vs. 76.9 ± 19.7mmHg, $p<.01$ respectively), as well as significantly lower left ventricular ejection fraction (LVEF) (38.8 ± 17.5% vs. 61.3 ± 12.9%, $p<.01$).

Perioperative Outcomes

The descriptive statistics and proportional difference between ECMO and non-ECMO patients are presented in Table 2. In general, perioperative outcomes were similar between ECMO and non-ECMO

patients. Valve migration or malpositioning, and VT or VF post-pacing were significantly more likely in ECMO patients as they were indications for rescue ECMO.

The rate of 30-day all-cause mortality was nil (0%) in the prophylactic ECMO patients, one (33%) in rescue ECMO patients, one (9%) in ECMO (prophylactic or rescue) patients, two (2%) in non-ECMO patients, and three (3%) for the series in total. The difference between ECMO and non-ECMO patients was not significantly different (9% vs. 2% $p>.05$). The one early mortality in the ECMO group was a patient that required rescue ECMO for rapid haemodynamic collapse after transfemoral TAVI implantation that was the result of aortic annulus rupture and tamponade. Emergent surgical drainage of the effusion was performed via left thoracotomy. Then a valve-in-valve implantation was performed which successfully sealed the annular leak, however the patient died on postoperative day 3 from systemic ischaemic complications [4]. The two early deaths in the non-ECMO group were a patient who died on postoperative day 25 from acute adrenal insufficiency after inadvertent chronic steroidal therapy suspension, and another patient who died on postoperative day 15 from complications related to the implantation (stroke, aspiration pneumonia).

In this series 11 (11%) patients developed acute renal failure (ARF) postoperatively: three rescue ECMO patients (100%), one prophylactic ECMO patient (12%), and seven (8%) non-ECMO patients. The results revealed that ECMO patients were significantly more likely to develop this complication than non-ECMO patients (36% vs. 8%, $p<.05$). The result held even after controlling for preoperative surgical risk (EuroSCORE) in logistic regression ($\exp[b] = 5.08$, $p<.05$). This difference also emerged as significantly more likely to occur in rescue than prophylactic ECMO patients (100% vs. 12%, $p<.05$). Indeed all three rescue ECMO patients experienced this outcome. One (33%) of the rescue ECMO patients and four (57%) of the non-ECMO patients had preoperative renal insufficiency (creatinine >110μmol/L).

Discussion

The present experience underscores how VA ECMO can be used to provide cardiorespiratory support during TAVI, in both prophylactic and emergent settings. TAVIs are performed at our institution by a Heart Team that involves close collaboration with anaesthetists and perfusionists to facilitate appropriate bail-out options in the event of complications. We prefer ECMO to a full cardiopulmonary bypass (CPB) circuit for reasons of space, reduced circuit prime, reduced activated clotting time requirement, and ease of use.

Multiple intraoperative complications can result in refractory low cardiac output or cardiogenic shock during TAVI, including spontaneous or post-pacing VF or VT, inadequate coronary artery perfusion due to low intra-aortic pressure or coronary ostia obstruction by the prosthesis, aortic root rupture causing tamponade, or severe bradycardia or AV block from prosthesis impingement on the conduction system following deployment. Additionally, patients with preexisting severe left or right ventricular dysfunction with pulmonary hypertension may not tolerate pacing during BAV or prosthesis implantation, resulting in haemodynamic collapse. If the underlying problem is not able to be resolved promptly and cardiac output does not respond to pharmacological management then a number of options are available as a bridge-to-recovery, including ventricular assist devices and ECMO [7,8]. At our institution no patient leaves the TAVI operating theatre whilst still on ECMO, as long-term ECMO in such a high-risk and elderly population has not been shown to change outcome. The use of VA ECMO for rescue of cardiogenic shock is being increasingly studied. A 2013 systematic review of ECMO in the context of refractory cardiac arrest concluded that in-hospital survival rates vary greatly from 6–59%, largely due to differences in patient selection [9]. Recently Kim and colleagues retrospectively reviewed 27 patients that required rescue ECMO for acute myocardial infarction complicated by cardiogenic shock: 82% of these patients were successfully weaned off ECMO, and 59% survived to discharge [10]. In the post-ECMO period 37% developed acute renal failure, and 37% developed pneumonia. They also found that a shorter period between CPR initiation and ECMO commencement resulted in better chance of successful weaning off ECMO ($p=0.006$), and that earlier weaning from ECMO yielded better outcomes. Lazzeri and colleagues' systematic review also found that outcomes depend heavily on the expertise of ECMO team [9].

In this series one patient experienced intraoperative cardiac tamponade as a result of aortic root rupture, that required rescue with ECMO. TAVI patients with bulky calcific leaflets and fragile tissue are particularly susceptible to aortic root injury during BAV or prosthesis implantation. Other possible causes of tamponade include injury to the right ventricle from perforation of the transient pacemaker wire, and injury to the left ventricle from stiff guide wires and catheters. In these patients if haemodynamic stability cannot be restored with pericardiocentesis or emergent sternotomy then rescue ECMO can be instituted until the issue is resolved. The valve should be deployed under ECMO cover and then the patient slowly weaned.

The analysis revealed that ECMO patients were significantly more likely to develop ARF than non-ECMO patients (36% vs. 8%, $p<.05$), especially if the ECMO was emergently instituted. Of the three rescue ECMO patients, two had VF post-pacing and thus experienced a period of systemic and renal hypoperfusion, which could have resulted in the ARF. ARF was also less common in prophylactic ECMO vs. rescue ECMO patients ($p<.05$), which suggests implementing ECMO before the need for rescue may help avoid this detrimental outcome. Other reasons for using rescue ECMO, including prosthesis migration, malpositioning, or aortic rupture, may require extra contrast usage which could also contribute to ARF. Another contributing factor was the incidence of the preoperative renal insufficiency, which was relatively common in the entire study population (55% of ECMO patients, and 52% of non-ECMO patients). A 2013 meta-analysis of 1,866 patients who received ECMO for cardiogenic shock found a cumulative rate of 55.6% of acute kidney injury (95% CI: 35.5 - 74.0%) (although studies used different definitions), and 46.0% of renal replacement therapy (95% CI: 36.7 - 55.5%) [11].

In this series the rate of early mortality at 30 days postoperatively was 9% in ECMO patients, 2% in non-ECMO patients, and 3% for the series in total. This is despite very high-risk patients: the mean EuroSCORE was 51.7 ± 24.9% in the ECMO patients and 30.8 ± 21.3% in the non-ECMO patients. Before and after controlling for this risk the rate of early mortality between the two groups was

similar. This early mortality rate is low compared to other reported studies: A 2013 meta-analysis comparing TAVI (n=1,688) to SAVR (n=1,777) found an all-cause mortality rate of 7.5% in TAVI patients [12]. Additionally, Husser and colleagues reported a rate of 22% in ECMO patients, which was significantly higher than their 5% rate in non-ECMO patients (p = .005) [13]. Their median logistic EuroSCORE was 26% (range 18–41) and 15% (range 9–22), respectively.

Our use of ECMO in the highest-risk cases was also much higher than reported in other TAVI series. Webb and colleagues reported that 4.1% of patients needed haemodynamic support in the Canadian series of 345 TAVI patients: 0.9% received haemodynamic support with intra-aortic balloon pump, 2.9% with ECMO, and 0.3% with both [14]. The reasons for haemodynamic support were all emergent: acute severe left ventricular dysfunction (2.9%), ventricular apical bleeding (0.9%), and cardiac perforation (0.3%), which may explain why haemodynamic support was significantly associated with higher 30 day mortality (OR: 6.8, 95% CI: 2.0-22.9, p = 0.002) and late mortality (HR: 2.6, 95% CI: 1.1-6). Additionally the IABP-SHOCKII trial has demonstrated that intra-aortic balloon pumps in patients with cardiogenic shock whilst undergoing revascularisation for myocardial infarction does not improve survival at 12 months (51.8% vs. 51.4%, p=0.91) [15].

Evidently the risk of providing prophylactic ECMO is much less than requiring emergent rescue with ECMO. As such, the low rate of early mortality during the early phase of our TAVI program may have been in part due to our high rate of prophylactic ECMO usage in the highest-risk patients (the mean EuroSCORE was 51.7 ± 24.9%). An example of this are two patients in this series who were on low-flow prophylactic ECMO support and experienced VT post-pacing, so ECMO flows were able to be increased and thus the patients experienced no circulatory arrest until cardioversion. Other published evidence for the reduction of early mortality or morbidity through the usage of prophylactic ECMO is thus far limited. Husser and colleagues used rescue ECMO in eight out of 131 cases for cardiogenic shock, VT and ventricular perforation [13]. After this they used prophylactic ECMO in nine high-risk patients, which resulted in higher procedural success (100% vs. 44% p=0.03) and lower early mortality (0% vs. 44% p=0.02), and similar rates of major vascular complications (11% vs. 11%,

p=0.99) or life-threatening bleeding (11% vs. 33%, p=0.3) [13].

Drews and colleagues reported using elective normothermic CPB in high-risk patients (EuroSCORE I 65 ± 23%) for similar reasons to our study, including preoperative cardiogenic shock (53%), severely depressed LV (37%) or RV (5%) function and pulmonary hypertension with enlarged RV (5%) [16]. Their strategy involved: placing the CPB tubes on the table in patients with pulmonary hypertension to save time if needed; to prophylactically cannulate the femoral vessels in patients with severely depressed LVEF (<25%) but only start CPB if they became unstable; and to perform valvuloplasty and valve deployment under a short run of CPB in patients with poor LV performance (LVEF 10–20%), cardiogenic shock or decompensated right-sided heart failure with an enlarged RV. The overall 30-day mortality rate in their cohort was 14%, all of which occurred in patients with preoperative cardiogenic shock, and was thus relatively low. The one- and two-year survival rates were 57 ± 8.4 and 49 ± 10%, respectively, and also significantly worse in those with cardiogenic shock [16].

Therefore, in our view this evidence suggests that prophylactic ECMO should be used more rather than less in the highest-risk patients, and we are looking prospectively to a create a defined scoring system to determine which patients receive prophylactic ECMO in TAVI at our institution.

Limitations

This study has a number of important limitations. As mentioned there was a small sample size of ECMO patients and thus it is difficult to draw definite conclusions from results. The study was also observational in nature. Whilst every effort was made to ensure data completeness and accuracy, some endpoints were missing small amounts of data, which was accounted for during the analysis.

Conclusion

ECMO, in both prophylactic and rescue settings, is effective at providing cardiorespiratory support in very-high risk TAVI patients, and may have contributed to the low mortality in this series. Instituting prophylactic ECMO in an elective, controlled setting may help avoid consequences of intraoperative

complications such as systemic hypoperfusion and ARF, compared to emergent ECMO with rapid setup and cannulation. In this clinical study, the criteria used to institute prophylactic ECMO were pre-operative assessment of moderate or severe left and/or right ventricular failure, difficulty with BAV performed to improve heart function pre-TAVI, and borderline haemodynamics at procedure. Future studies performed in a prospective, randomised fashion are required to evaluate the use of prophylactic ECMO, and to determine the ideal selection criteria.

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Tables

Table 1: Baseline characteristics of patients who received ECMO.

	Prophylactic ECMO (n = 8)	Rescue ECMO (n = 3)	ECMO (combined) (n = 11)	Non-ECMO (n = 89)	ECMO vs. Non-ECMO Difference[a]
Logistic EuroSCORE I (%)	49.29 ± 24.65	58.24 ± 29.98	51.73 ± 24.95	30.81 ± 21.32	20.92*
Age (yrs)	75.62 ± 10.01	76.00 ± 8.00	75.73 ± 9.11	83.52 ± 8.55	-7.79*
Male	6 (75%)	2 (67%)	8 (73%)	55 (62%)	11%
Body mass index (kg/m^2)	25.51 ± 1.97	31.67 ± 8.93	27.56 ± 5.64	26.05 ± 4.94	1.51
NYHA class III or IV	8 (100%)	3 (100%)	11 (100%)	74 (83%)	0.17
Moderate-severe lung disease	0 (0%)	2 (67%)	2 (18%)	10 (11%)	0.07
History of smoking	6 (75%)	2 (67%)	8 (73%)	55 (62%)	0.11
Hypertension	8 (100%)	3 (100%)	11 (100%)	77 (87%)	0.13
Hyperlipidaemia	4 (50%)	2 (67%)	6 (55%)	43 (48%)	0.07
Diabetes mellitus	3 (38%)	0 (0%)	3 (27%)	14 (16%)	0.11
Previous myocardial infarction	6 (75%)	2 (67%)	8 (73%)	23 (26%)	47%**
Previous CABG	6 (75%)	3 (100%)	9 (82%)	30 (34%)	48%**
Previous PCI	1 (12%)	0 (0%)	1 (9%)	28 (31%)	-0.22
Previous balloon aortic valvuloplasty	4 (50%)	0 (0%)	4 (36%)	17 (19%)	0.17
Cerebrovascular disease	2 (25%)	2 (67%)	4 (36%)	24 (27%)	0.09
Peripheral vascular disease	2 (29%)	2 (67%)	4 (40%)	26 (29%)	0.11
Renal insufficiency[b]	5 (62%)	1 (33%)	6 (55%)	46 (52%)	0.03
Patients on dialysis	1 (12%)	0 (0%)	1 (9%)	4 (4%)	0.05
Atrial fibrillation	0.25 ± 0.46	0.00 ± 0.00	0.18 ± 0.40	0.36 ± 0.48	-0.18
Echocardiography					
Mean transaortic gradient (mmHg)	40.14 ± 9.30	38.67 ± 1.53	39.70 + 7.66	45.96 ± 12.52	-6.26*
Peak transaortic gradient (mmHg)	58.86 ± 17.03	62.00 ± 4.36	59.80 ± 14.14	76.94 ± 19.72	-17.14**

Aortic valve area (cm^2)	0.64 ± 0.13	0.63 ± 0.06	0.64 ± 0.11	0.73 ± 0.23	-0.09†
LVEF (%)	32.33 ± 7.47	58.00 ± 29.70	38.75 ± 17.52	61.25 ± 12.95	-22.50**
Mean PA pressure	40.71 ± 10.58	35.00 ± 14.14	39.44 ± 10.74	30.42 ± 9.20	9.03*
Systolic PA pressure ≥60mmHg	4 (57%)	2 (100%)	6 (67%)	14 (20%)	47%**
Right ventricular dysfunction	4 (50%)	2 (67%)	6 (55%)	3 (3%)	52%**
Mild	2 (25%)	1 (33%)	3 (27%)	2 (2%)	
Moderate	2 (25%)	1 (33%)	3 (27%)	0 (0%)	
Severe	0 (0%)	0 (0%)	0 (0%)	1 (1%)	

Descriptive Statistics presented as *n* (%) or mean ± standard deviation as appropriate. NYHA = New York Heart Association; CABG = Coronary Artery Bypass Graft; PCI = Percutaneous Coronary Intervention; PA = Pulmonary artery; LVEF = Left ventricular ejection fraction

**$p < .01$, * $p < .05$, † $p < .10$

[a]Test is t-test for continuous variable; Chi-Square for categorical

[b]defined as creatinine >100µmol/L

Table 2: Perioperative outcomes of patients who received ECMO.

	Prophylactic ECMO (*n* = 8)	Rescue ECMO (*n* = 3)	ECMO (combined) (*n* = 11)	Non-ECMO (*n* = 89)	ECMO vs. Non-ECMO Difference[a]
Intraoperative outcomes					
Conversion to open procedure	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0%
Valve migration or malpositioning	1 (12%)	1 (33%)	2 (18%)	2 (3%)	15%
Coronary ostia obstruction	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0%
VT/VF post pacing	2 (25%)	2 (67%)	4 (36%)	2 (2%)	34%**
Delayed closure	1 (12%)	0 (0%)	1 (9%)	1 (1%)	8%
30 day outcomes					
All-cause mortality	0 (0%)	1 (33%)	1 (9%)	2 (2%)	7%
Cardiovascular mortality	0 (0%)	1 (33%)	1 (9%)	1 (1%)	8%
Peri-procedural MI (<72hrs)	0 (0%)	0 (0%)	0 (0%)	2 (2%)	-2%
Spontaneous MI (>72hrs)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0%
Disabling Stroke	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0%
Non-disabling Stroke	0 (0%)	0 (0%)	0 (0%)	2 (2%)	-2%
Transient ischaemic attack	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0%
Life-threatening bleeding	1 (12%)	1 (33%)	2 (18%)	3 (3%)	15%
Major bleeding	0 (0%)	1 (33%)	1 (9%)	10 (12%)	-3%
Minor bleeding	3 (38%)	0 (0%)	3 (27%)	11 (13%)	14%
Acute renal failure	1 (12%)	3 (100%)[b]	4 (36%)	7 (8%)	28%*
Major vascular complications	1 (12%)	1 (33%)	2 (18%)	4 (5%)	13%
Minor vascular complications	0 (0%)	0 (0%)	0 (0%)	11 (13%)	-13%
Need for permanent pacemaker	2 (25%)	1 (33%)	3 (27%)	12 (13%)	14%
Postoperative atrial fibrillation	1 (12%)	0 (0%)	1 (9%)	5 (6%)	3%

Descriptive Statistics presented as *n* (%). MI = Myocardial Infarction.

**$p < .01$, * $p < .05$, † $p < .10$

[a]Chi-Square test

[b]p(Rescue = Support) < .05