High-risk cardiac surgery as an alternative to transplant or mechanical support in patients with end-stage heart failure

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ABSTRACT

Objective: Although the results of cardiac surgery in patients with poor left ventricular function have been widely published, the outcomes in patients with end-stage heart failure who meet criteria for advanced therapies are not well investigated. As access to transplantation and ventricular assist device therapy remains limited, we explored the possibility of conventional surgery as an alternative option for highly selected patients with end-stage heart failure.

Methods: We identified patients with left ventricular ejection fraction <20% and $\text{VO}_2 \text{ max} < 14 \text{ mL/min/m}^2$, who were initially referred for advanced therapies but were instead offered a conventional procedure from 2002 to 2012. We examined the short- and midterm outcomes and compared survival with that after our advanced therapies in the same era.

Results: A total of 133 patients were identified; 68 were deemed to be transplant-eligible, whereas 65 were transplant-ineligible. Seventy-nine percent were in New York Heart Association class III/IV. In-hospital mortality was 12%. Actuarial survival at 5 and 10 years was $72\% \pm 4\%$ and $39\% \pm 8\%$, respectively. Non-ischemic etiology was identified as a predictor of late mortality. In the propensity-adjusted model, our transplant-eligible patients had comparable long-term survival to our transplantation patients (HR 1.48 [95% confidence interval, 0.66-3.2], $P = .34$), whereas the survival in our transplant-ineligible subset was comparable to the survival after our left ventricular assist device therapy (HR 0.49 [95% confidence interval, 0.16-1.50], $P = .21$).

Conclusions: Despite high perioperative risk, the midterm survival after conventional surgery in patients eligible for advanced therapies seems to be acceptable and may be an alternative option for highly selected patients with end-stage heart failure. (J Thorac Cardiovasc Surg 2017;154:517-25)

Long-term survival after conventional surgeries for end-stage heart failure patients.

Central Message

High-risk conventional cardiac surgery provides acceptable midterm survival for highly selected patients with end-stage heart failure.

Perspective

There is a spectrum of patients with poor left ventricular ejection fraction who present for surgical consideration, a subset of whom are initially referred for transplantation or ventricular assist device. We found that conventional cardiac surgery in this subgroup of patients provided acceptable midterm survival and may be a suitable option for highly selected patients with end-stage heart failure.

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Although many preventive and pharmacological approaches have been introduced, more than 650,000 new patients with heart failure (HF) are diagnosed annually in the

United States and the prevalence is still rising.¹ The most definitive treatment for refractory end-stage HF has been heart transplantation (HTx); however, donor scarcity still remains a critical issue and waiting times to transplantation continue to increase.² Left ventricular assist devices (LVAD) were initially introduced as a bridge to transplantation, but more recently most LVAD recipients represent

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Abbreviations and Acronyms

AV	= aortic valve
BTT	= bridge-to-transplant
CABG	= coronary artery bypass grafting
CI	= confidence interval
DCM	= dilated cardiomyopathy
DT	= destination therapy
HF	= heart failure
HR	= hazard ratios
HRS	= high-risk conventional surgery
HTx	= heart transplantation
IABP	= Intra-aortic balloon pump
INTERMACS	= Interagency Registry for Mechanically Assisted Circulatory Support
ISHLT	= International Society for Heart and Lung Transplantation
LVAD	= left ventricular assist devices
LVDd	= left ventricular end-diastolic diameter
LVEF	= left ventricular ejection fraction
MV	= mitral valve
NYHA	= New York Heart Association
VO ₂ max	= maximal oxygen consumption

“destination therapy (DT)” and are HTx ineligible.^{3,4} Although DT-LVAD is now widely accepted as an alternative advanced surgical option for patients with end-stage HF, they remain associated with a high adverse event rate and few patients survive event-free beyond 5 years.⁵

Because of the marked limitations in both of these advanced surgical therapies, surgeons are often forced to make a difficult decision when they encounter patients with end-stage HF who have cardiac lesions amenable to conventional surgery. Although the immediate perioperative risk is widely recognized, the long-term benefit of conventional surgeries for this extreme subset is less well characterized.⁶ In addition, most of the studies investigating the outcomes of “high-risk” cardiac surgeries used only left ventricular ejection fraction (LVEF) as an inclusion criteria,⁷⁻¹⁵ but LVEF alone may not be adequate to identify end-stage HF.^{1,16} Therefore, we investigated the outcomes of conventional cardiac surgery in patients who met the criteria for advanced surgical therapies to explore its possibility as an alternative option for end-stage HF.

METHODS**Patient Enrollment**

We reviewed our institutional database to find all surgical patients who had a preoperative LVEF <20% (n = 648) from May 2002 to Apr 2012. Among them, we identified 377 patients who were initially referred to our HF team for advanced surgical therapies, including HTx or any strategy of LVAD therapy.

Although the 271 excluded patients who were directly referred for conventional cardiac surgeries were not specifically reviewed, these likely represented patients with acute-onset disease in whom myocardial function was expected to recover after surgical intervention (ie, stunned myocardium after acute myocardial infarction or high-gradient aortic stenosis). Alternatively, these patients may have not met inclusion criteria for transplantation (maximal oxygen consumption [VO₂ max] > 14). The remaining 377 patients underwent 434 procedures, which were classified according to primary therapy and intention-to-treat. A first group of 133 patients underwent high-risk conventional surgery (HRS) of whom 68 were transplant candidates and 65 were not. Those operations included coronary artery bypass grafting (CABG), valve intervention, and LV reconstruction; 2 of these patients eventually underwent HTx. The second group included 208 patients who were eligible for transplant and underwent HTx or bridge-to-transplant (BTT-) LVAD as their primary therapy (155 HTx and 53 BTT-VAD). Twenty-eight patients with BTT-VAD eventually underwent HTx during their follow-up. The third and final group included 36 patients who were not eligible for transplantation and underwent LVAD implantation as DT (Figure 1).

Eligibility for Advanced Surgical Therapies

All 377 (133 HRS, 208 HTx/BTT-VAD, 36 non-BTT-VAD) enrolled patients were initially referred for advanced surgical therapies and their eligibility for these therapies was preoperatively evaluated by our multidisciplinary HF team based on standard criteria.^{1,6,17} Briefly, patients were subjected to formal cardiopulmonary testing to determine functional capacity. A VO₂ max of 14 mL/min/m² was used as a cutoff to determine the need for advanced therapies. HTx eligibility was assessed by additional screening for peripheral vascular disease, pulmonary hypertension, and other comorbidities. Among the 133 patients in the HRS group, 65 patients (49%) were deemed to be HTx-ineligible, and 68 (51%) were HTx-eligible (Figure 1).

Patient Selection for HRS

Patient selection for HRS was made on a case-by-case basis during our multidisciplinary HF team conference in consideration of the risk, patient's body habitus, and the potential of myocardial recovery. In patients with ischemic cardiomyopathy, myocardial viability was assessed by late gadolinium-enhanced magnetic resonance imaging or single-photon-emission computed tomography to determine the potential of recovery. We considered revascularization if patients had at least 1 good coronary target with a tight proximal lesion. Nonviable myocardium in a left anterior descending artery distribution was not necessarily an exclusion criterion if there was viable myocardium in other coronary distributions and/or LV reconstruction was possible. In valve surgery patients, our accrued experience during this time frame led us to avoid mitral valve (MV) surgery in patients with an LV end-diastolic diameter (LVDd) >65 mm.¹⁸ Dobutamine stress echocardiography was performed for aortic valve (AV) surgery patients to determine their functional reserve and to stratify their risk. Patients who had a history of myocardial infarction and akinetic or dyskinetic LV aneurysms were considered for LV reconstruction as previously described.^{19,20}

Data Collection

All perioperative and demographic data were routinely abstracted from the patient chart and collected prospectively in our institution's surgical database. Follow-up data were obtained from the surgeon's office chart, our electronic medical record, or by contact with the patient's referring cardiologist. Clinical follow-up was 100% complete.

Statistical Analysis

In-hospital mortality was defined as any death occurring during the index hospital admission or within 30 days of surgery.²¹ All data are described as means with standard deviations, median with 25th and 75th percentiles, and frequencies, as appropriate. A prespecified subgroup

FIGURE 1. Description of patient enrollment. *LVEF*, Left ventricular ejection fraction; *VO₂ max*, maximal oxygen consumption; *HRS*, high-risk conventional surgery; *HTx*, heart transplantation; *BTT*, bridge-to-transplant; *VAD*, ventricular assist device.

analysis was performed comparing patients who were HTx-eligible with those who were not by using Fisher exact test, Student *t* test assuming unequal variance between study groups (Satterthwaite method), and Cox regression models, as appropriate.

A propensity score was generated to determine the probability of patients to undergo high-risk surgery instead of advanced support. First, patients eligible for HTx who underwent high-risk operations were compared with patients who underwent HTx or BTT-VAD and then, patients who underwent high-risk operations but were not eligible for HTx were compared with patients who underwent non-BTT-LVAD implantation. The propensity score in both cases was based on 8 variables selected for their clinical relevance: age, gender, New York Heart Association (NYHA) classification, hypertension, creatinine, diabetes, atrial fibrillation, and hypercholesterolemia. Both propensity scores achieved a high degree of segregation (*c*-statistics >0.85 in both cases), hence direct matching was not possible. Survival between patients undergoing high-risk operations and their respective controls based on patient eligibility was compared by using Cox regression models using both unadjusted and propensity-adjusted models. As we aimed to compare the surgical outcomes of each approach instead of overall outcomes, we defined time zero as the date of first surgery, not the date of decision. Patient survival stratified by HTx eligibility is reported along with the contemporary data of adult HTx and DT-LVAD from the International Society for Heart and Lung Transplantation (ISHLT) and Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) for qualitative comparison.²²⁻²⁶

All statistical analyses were performed using SAS v9.3 (SAS Institute, Inc, Cary, NC). The study was approved by the local ethics committee of our institution, and written informed consent was waived because of the retrospective nature of this study.

RESULTS

Patient Characteristics of HRS

Patient demographics and surgical characteristics of our HRS group are presented in Table 1. The mean age was

63 ± 10 years and 83% were men. All patients had LVEF <20% and *VO₂ max* <14 mL/min/m², and 79% of patients were NYHA class III/IV. The etiology of HF was ischemic in 121 (91%), valvular in 4 (3%), and 8 (6%) patients presented with idiopathic dilated cardiomyopathy (DCM). The primary lesions for surgical interventions in valvular patients were aortic stenosis (*n* = 3) and aortic regurgitation (*n* = 1). Patients felt to have DCM were also found to have low-flow, low-gradient aortic stenosis (*n* = 5) or aortic regurgitation (*n* = 1), and 2 (25%) patients underwent repair for functional mitral regurgitation. The perioperative risk calculated by EuroSCORE II scoring system in our population was 11.3% ± 10.8%.

As expected, HTx-ineligible patients were older than HTx-eligible patients (70 ± 8 vs 57 ± 8 years, *P* < .001). HTx-ineligible patients had more comorbidities including peripheral vascular disease (29% vs 12%, *P* = .02), higher serum creatinine levels (111 ± 57 vs 96 ± 24 μmol/L, *P* = .04), and chronic obstructive pulmonary disease (11% vs 3%, *P* = .09). Most HF etiology was ischemic in both groups (90% vs 92%, *P* = .76). The EuroSCORE II perioperative risk was significantly higher in HTx-ineligible patients compared with HTx-eligible patients (13.9 ± 13.0 vs 8.9 ± 7.4, *P* = .007).

Short- and Midterm Outcomes of HRS

Table 2 displays overall short- and midterm outcomes of our HRS group. In total, the in-hospital mortality was 12% (*n* = 16). Ten cases (63%) were due to low-output

TABLE 1. Patient and surgical characteristics of high-risk conventional surgery

Variables	All (n = 133)	HTx-eligible (n = 68)	HTx-ineligible (n = 65)	P
Patient characteristics				
Age, y, mean $\pm$ SD	63 $\pm$ 10	57 $\pm$ 8	70 $\pm$ 8	<.001
Sex, male	110 (83)	57 (84)	53 (82)	.82
NYHA class				.08
III	52 (39)	26 (38)	26 (41)	
IV	52 (39)	32 (47)	20 (31)	
Left ventricular grade 4 (LVEF <20%)	133 (100)	68 (100)	65 (100)	n.a.
Heart transplantation eligibility (Yes)	68 (51)	68 (100)	0 (0)	n.a.
Etiology of heart failure				
Ischemic	121 (91)	61 (90)	60 (92)	
Valvular	4 (3)	0 (0.0)	4 (6)	
Aortic stenosis	3 (75)	0 (0.0)	3 (75)	
Aortic regurgitation	1 (25)	0 (0.0)	1 (25)	
Dilated cardiomyopathy	8 (6)	7 (10)	1 (2)	
Aortic stenosis	5 (63)	4 (57)	1 (100)	
Aortic regurgitation	1 (13)	1 (14)	0 (0)	
Functional mitral regurgitation	2 (25)	2 (29)	0 (0)	
Atrial fibrillation or flutter	15 (11)	6 (9)	9 (14)	.42
Diabetes mellitus	65 (49)	35 (52)	30 (46)	.60
Medically treated hypertension	77 (58)	35 (52)	42 (65)	.16
Diet or medically treated hyperlipidemia	103 (77)	52 (77)	51 (79)	.84
Family history heart disease	58 (44)	31 (46)	27 (42)	.73
Smoking history	97 (73)	47 (69)	50 (77)	.34
Dialysis	1 (0.8)	0 (0)	1 (2)	.49
Chronic obstructive pulmonary syndrome	9 (7)	2 (3)	7 (11)	.09
Previous stroke or trans-ischemic attack	16 (12)	7 (10)	9 (14)	.60
Peripheral vascular disease	27 (20)	8 (12)	19 (29)	.02
Carotid stenosis >70% (unilateral + bilateral)	8 (6)	2 (3)	6 (9)	.16
Serum creatinine level, μ mol/L	103 $\pm$ 45	96 $\pm$ 24	111 $\pm$ 57	.04
Previous cardiac surgery	5 (4)	3 (4)	2 (3)	1.00
Myocardial infarction within 30 d	26 (20)	11 (16)	15 (23)	.38
EuroSCORE II	11.3 $\pm$ 10.8	8.9 $\pm$ 7.4	13.9 $\pm$ 13.0	.007
Surgical characteristics				
Urgent/Emergent surgery	5 (4)	2 (3)	3 (5)	.48
CABG	122 (92)	62 (91)	60 (93)	1.00
Total number of distal grafts				.25
1	10 (8)	4 (6)	6 (10)	
2	14 (11)	5 (8)	9 (15)	
3	35 (29)	17 (27)	18 (30)	
4+	63 (52)	36 (58)	27 (45)	
Aortic valve surgery	16 (12)	6 (9)	10 (15)	.29
Mitral valve surgery	42 (32)	27 (40)	15 (23)	.002
Repair	37 (88)	25 (93)	12 (80)	
Replacement	5 (11)	2 (7)	3 (20)	
Tricuspid valve surgery	6 (5)	5 (7)	1 (2)	.21
Left ventricular reconstruction	51 (38)	29 (43)	22 (34)	.37
Cardiopulmonary bypass time, min	113 $\pm$ 33	113 $\pm$ 32	112 $\pm$ 34	.76
Cross-clamp time, min	82 $\pm$ 31	87 $\pm$ 25	77 $\pm$ 35	.06

Values are n (%) unless otherwise indicated. HTx, Heart transplantation; SD, standard deviation; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; n.a., not applicable because the groups were either identical or completely disparate; CABG, coronary artery bypass grafting.

syndrome (LOS). Among the 16 deaths, 15 were ischemic and 1 dilated cardiomyopathy patients. Among the patients with ischemic etiology, the in-hospital mortality with corresponding EuroSCORE II of isolated CABG (n = 43), CABG + LV reconstruction (n = 34), CABG + MV $\pm$

tricuspid valve (n = 21), CABG + LV reconstruction + MV (n = 15) was 2.3% (8.0% $\pm$ 7.1%), 11.8% (12.2% $\pm$ 13.7%), 14.3% (11.2% $\pm$ 7.0%), and 20.0% (18.7% $\pm$ 10.3%), respectively. The in-hospital mortality of isolated CABG was significantly lower than that of any

TABLE 2. Short- and midterm outcomes of high-risk conventional surgery

Variables	All (n = 133)	HTx-eligible (n = 68)	HTx-ineligible (n = 65)	P
Short-term outcomes				
Ventilation time, h (range)	9 (6-19)	8 (5-19)	11 (6-24)	.34
ICU stay, h (range)	74 (41-138)	69 (26-130)	74 (23-142)	.86
Hospital stay, d (range)	9 (7-13)	8 (6-12)	9 (6-13)	.83
Insertion of IABP	22 (17%)	11 (16%)	11 (17%)	1.00
Reoperation for bleeding	9 (7%)	4 (6%)	5 (8%)	.74
High-dose dopamine use	68 (51%)	32 (47%)	36 (55%)	.39
Low-output syndrome	23 (17%)	10 (15%)	13 (20%)	.49
Renal failure (dialysis required)	5 (4%)	3 (4%)	2 (3%)	1.00
Pulmonary complications	31 (23%)	15 (22%)	16 (25%)	.84
Persistent neurological deficit	3 (2%)	0 (0%)	3 (5%)	.20
Sternal infection	3 (2%)	2 (3%)	1 (2%)	1.00
Mortality	16 (12%)	6 (9%)	10 (15%)	.29
LOS	10 (63%)	4 (67%)	6 (60%)	
MOF	2 (13%)	0 (0%)	2 (20%)	
Arrhythmia	1 (6%)	0 (0%)	1 (10%)	
Sepsis	1 (6%)	1 (17%)	0 (0%)	
Pneumonia	1 (6%)	1 (17%)	0 (0%)	
Unknown	1 (6%)	0 (0%)	1 (10%)	
Midterm outcomes				
Duration of follow-up, y (range)	4.9 (2.3-7.1)	4.7 (2.3-7.2)	3.7 (0.9-6.7)	.10
Mortality	46 (35%)	16 (24%)	30 (46%)	.01
Cardiac cause	20 (44%)	9 (56%)	11 (37%)	
Noncardiac cause	12 (26%)	4 (25%)	8 (27%)	
Unknown	14 (30%)	3 (19%)	11 (37%)	
NYHA class at last follow-up				.82
I	28 (29%)	16 (30%)	12 (29%)	
II	39 (41%)	21 (39%)	18 (43%)	
III	28 (29%)	17 (32%)	11 (26%)	
IV	1 (1%)	0 (0%)	1 (2%)	
Hospitalization for heart failure	22 (19%)	13 (21%)	9 (16%)	.64

Values are n (%) unless otherwise indicated. HTx, Heart transplantation; ICU, intensive care unit; IABP, intra-aortic balloon pumping; LOS, low-output syndrome; MOF, multiple organ failure; NYHA, New York Heart Association.

combined procedures (2.3% vs 14.3%, $P = .03$). The median (interquartile range) durations of intensive care unit and hospital stay were 74 (41-138) hours and 9⁷⁻¹³ days, respectively. Intra-aortic balloon pump (IABP) support was required in 17% ($n = 22$) postoperatively. After a median follow-up of 4.9 years (range 0 days to 11 years), 46 patients (35%) were deceased. Survival at 5 and 10 years was $72\% \pm 4\%$ and $39\% \pm 8\%$. Notably, NYHA class at last follow-up was significantly improved from preoperative grade. In the comparison between the 2 subsets in our HRS group, there was no significant difference in the incidence of postoperative complications. Midterm mortality was significantly higher in HTx-ineligible patients (HR 2.37 [95% confidence interval (CI), 1.29-4.38], $P = .006$). NYHA class was considerably improved from preoperative grade in both subsets.

Figures 2 and 3 illustrate the comparison of the survival curves between our HRS and advanced therapy groups. The patient demographics used for the adjustment in all groups are displayed in Table 3. The contemporary data

of adult HTx and DT-LVAD from ISHLT and INTERMACS was also superimposed for comparison.^{22,23} As shown in Figure 2, our HTx-eligible HRS patients had comparable long-term survival to our HTx/BTT-VAD patients (unadjusted HR 0.97 [95% CI, 0.55-1.69], $P = .91$; propensity-adjusted HR 1.48 [95% CI, 0.66-3.29], $P = .34$). Similarly in Figure 3, the survival of our HTx-ineligible HRS patients was comparable to the survival after our non-BTT-LVAD therapy (unadjusted HR 0.57 [95% CI, 0.32-1.02], $P = .06$; propensity-adjusted HR 0.49 [95% CI, 0.16-1.50], $P = .21$).

Independent Risk Factors for Survival Outcome of HRS

The multivariable analysis of variables associated with long-term mortality is presented in Table 4. In addition to HTx ineligibility, nonischemic HF etiology was identified as an independent risk factor. Nonelective surgery, higher preoperative creatinine, and longer cardiopulmonary bypass time also correlated with long-term mortality.

FIGURE 2. Comparison of the survival curves between our high-risk conventional surgery (HRS) for transplant-eligible patients and heart transplantation (HTx) or bridge-to-transplant left ventricular assist device (BTT-LVAD) patients, benchmarked to contemporary adult HTx data from International Society for Heart and Lung Transplantation (ISHLT).²² The index event was defined as the time of first surgery. HR, Hazard ratio.

DISCUSSION

Patient Population

This study investigated the outcomes of conventional cardiac surgery in patients with end-stage HF who would otherwise have been listed for HTx or offered LVAD support. Although there are many studies reporting the

outcomes of cardiac surgery in patients with low LVEF,^{7-15,20,27-29} the current study represents an extreme subset that met functional criteria for advanced surgical therapies ($\text{VO}_2 \text{ max} < 14 \text{ mL/min/m}^2$). Although many patients with LVEF $< 20\%$ did indeed proceed to heart transplant and/or LVAD, 404 patients underwent

FIGURE 3. Comparison of the survival curves between our high-risk conventional surgery (HRS) for transplant-ineligible patients and non-bridge-to-transplant left ventricular assist device (non-BTT-LVAD), benchmarked to contemporary LVAD destination therapy data from Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS).²³ The index event was defined as the time of first surgery. HR, Hazard ratio.

TABLE 3. Patient demographics of high-risk conventional surgery and advanced surgical therapies used for propensity score adjustment

Variables	HTx-eligible (n = 68)	BTT-LVAD/HTx (n = 208)	HTx-ineligible (n = 65)	Non-BTT-LVAD (n = 36)
Age, y, mean $\pm$ SD	57 $\pm$ 8	48 $\pm$ 12	70 $\pm$ 8	49 $\pm$ 14
Sex, male	57 (84)	139 (67)	53 (82)	27 (75)
NYHA class				
III	26 (38)	53 (27)	26 (39)	5 (14)
IV	32 (48)	126 (65)	20 (31)	22 (63)
Hypertension	35 (51)	29 (14)	42 (65)	5 (14)
Creatinine, μ mol/L, mean $\pm$ SD	96 $\pm$ 24	122 $\pm$ 92	111 $\pm$ 57	142 $\pm$ 61
Diabetes	35 (51)	35 (17)	30 (46)	10 (28)
Atrial fibrillation	15 (22)	27 (13)	29 (45)	12 (34)
Hypercholesterolemia	51 (78)	60 (29)	51 (78)	12 (33)

Values are n (%) unless otherwise indicated. HTx, Heart transplantation; BTT, bridge-to-transplant; LVAD, left ventricular assist device; SD, standard deviation; NYHA, New York Heart Association.

conventional surgery. Only 133 (33%) of these patients met inclusion criteria for our study (VO_2 max <14), underscoring the fact that these patients are an extreme subset of patients with LV dysfunction.

According to the 2013 American College of Cardiology Foundation/American Heart Association Guidelines for the Management of Heart Failure, the general indications for referral for mechanical circulatory support include patients with LVEF $<25\%$ and NYHA class III-IV (Class IIa, Evidence level B).¹ In the present study, all patients had LVEF $<20\%$ and the percentage of NYHA class III/IV was 79%. Maltais et al¹³ reported their acceptable outcomes of a combined CABG and MV surgery in patients with severe ischemic cardiomyopathy compared with their DT-LVAD results. In their study, they used LVEF $<25\%$ as an inclusion criterion for the conventional surgery group to match up with their DT-LVAD population; however, other parameters indicating HF grade or functional capacity were not reported. Kainuma et al²⁸ reported their outcomes of MV repair for functional MV regurgitation in patients with advanced HF. In their study, all patients had stage C/D HF symptoms and 91% were in NYHA class III/IV; nevertheless, their LVEF cutoff value was 40%. Thus, we believe that our study has investigated the outcomes of conventional surgery in an advanced HF population compared with other published studies. Importantly, in addition to poor EF ($<20\%$), we included an objective criterion (VO_2 max <14 mL/min/m²) and the subjective referral of these patients to our HF team for consideration of advanced therapies.

In the present study, an ischemic etiology was evident in more than 90% of the patients. According to a large observational study of HF in a general population in the United Kingdom, coronary artery disease is the cause of 52% of HF in patients younger than 75, followed by 13% idiopathic and 10% valvular diseases.³⁰ This discrepancy in the proportion of HF etiology between our surgical patients and the general population in the United Kingdom likely reflects our bias to offer surgery to patients with ischemic heart disease.

Despite an overwhelming ischemic population, a large proportion underwent MV surgery (32%). Not surprisingly, LV reconstruction was also performed in 38% of this cohort. A previous report from our group has identified that the combination of LV repair and MV intervention is associated with high mortality and morbidity.¹⁸ This prior study did not restrict inclusion to patients meeting criteria for advanced therapy and, as such, it is not surprising that the overall mortality in our current study is relatively high at 12%. Fedoruk et al²⁷ described that they performed 25% concomitant MV surgery and 17% LV remodeling surgery in their patients with ischemic cardiomyopathy with LVEF $<35\%$ with an overall mortality of 8%. These numbers suggest that our patients were more advanced in terms of HF stage as well as LV remodeling.

Outcomes of HRS for Patients With End-Stage HF

Our 5-year survival ($72\% \pm 4\%$) was comparable with previous studies.^{7,9,11,13-15,28} Kunadian et al⁷ conducted a meta-analysis of 26 nonrandomized studies with 4119 cases involving isolated CABG for patients with LVEF $<35\%$ and the overall 5-year survival was 73%. Again, these studies included a wide range of patients with “LV dysfunction” and no study isolated their analyses to an advanced therapy-eligible population. Ahmed et al¹¹ studied the outcomes of isolated CABG in 162 patients with LVEF $<30\%$ and their 5-year survival was 69%. Kainuma et al²⁸ reported their results with MV surgery $\pm$ CABG $\pm$ surgical ventricular reconstruction for 208 patients with advanced cardiomyopathy with LVEF $<40\%$ and end-systolic volume >60 mL/m². Their 5-year survival stratified by renal function was 77%, 45%, and 70% in normal, severely impaired, and hemodialysis patients, respectively. Halkos et al¹⁴ also described their outcomes for 773 AV replacements for aortic stenosis $\pm$ CABG and the 5-year survival rate in patients with LVEF $<40\%$ was 62%.

The STICH trial was designed to determine the benefit of CABG in patients with LV dysfunction due to ischemic cardiomyopathy.²⁹ Although the primary outcome analysis failed to show a superiority of CABG compared with

TABLE 4. Independent risk factors for long-term mortality of high-risk conventional surgery

Risk factor	HR (95% CI)	P
Transplant-eligible	0.40 (0.20-0.80)	.01
Nonischemic etiology of heart failure	2.82 (1.00-7.94)	.05
Nonelective surgery	2.10 (1.13-3.88)	.02
Preoperative creatinine		
>150 μ mol/L	3.82 (1.55-9.39)	.003
100-149 μ mol/L	1.98 (1.00-3.92)	.05
<100 μ mol/L	Reference	
Longer cardiopulmonary bypass time (per 30 min)	1.49 (1.11-2.00)	.05

HR, Hazard ratio; CI, confidence interval.

medical therapy alone, it is difficult to compare the findings with our study because the profiles of our patients were much sicker than the ones in STICH. For example, the LVEF cutoff in the STICH trial was 35% and most of them had NYHA class II or III symptoms (class II 50%, III 35%). In addition, most investigators believe that the high crossover rate from medical therapy to surgery in the first year after randomization significantly confounded the interpretation of the STICH study. Indeed, a post hoc analysis examining “as-treated” patients revealed a significant benefit to surgical intervention with respect to overall mortality and freedom from repeat hospitalization. Our results suggest that even in a higher risk surgical population, the benefits of surgical revascularization lead to higher than expected survival.

As we expected, our in-hospital mortality (12%) seemed to be relatively high given that the mortality in the previous studies ranged between 5% and 11%.^{7,9,11,13-15,27,28} The incidence of other postoperative complications was similar (16%-20% need for IABP, 4%-6% reoperation for bleeding, 4%-5% neurological deficit). We believe that this modestly higher early mortality reflects the advanced disease state in our population and the complexity of the surgery. Indeed, the calculated perioperative risk using the EuroSCORE II scoring system in our population was $11.3\% \pm 10.8\%$, and that was very close to our observed early mortality. In addition, the early mortality in our isolated patients with CABG was significantly lower than the one in the patients who underwent any combined procedures (2.3% vs 14.3%, $P = .03$). Interestingly, the mortality was much lower than their estimated risk by EuroSCORE ($8.0\% \pm 7.1\%$). More importantly, our long-term results indicate that once these patients are through the high-risk perioperative course, they continue on with reasonably acceptable survival.

Because our HRS and advanced surgical therapy groups had different patient demographics, we used propensity adjustment to compare the survival outcome instead of matching, as described in Method section. Of note, the results of comparisons in propensity-matched small subsets

were essentially similar to those of the propensity-adjusted model (data not shown). Both in unadjusted and adjusted models, the survival after our HRS in HTx-eligible patients was comparable to our HTx/BTT-VAD survival. In addition, the HTx-ineligible subset in our HRS group had comparable survival to our non-BTT-LVAD patients. These results suggest that HRS may be an alternative option to the advanced surgical therapies for highly selected patients with end-stage HF.

Patient Selection for HRS

In addition to conventional risk (eg, frailty, comorbidities) and potential of myocardial recovery (eg, myocardial viability and functional reserve), the etiology of HF may also need to be considered before offering conventional surgeries for patients with end-stage HF. Our results identified that patients with ischemic HF had more favorable midterm survival than other cardiomyopathies. On the other hand, it is known that the short- and long-term mortality after HTx in ischemic etiology recipients is higher than other groups.²² Patients with ischemic HF also have a higher mortality while waiting for HTx compared with nonischemic patients.³¹ Taken together, patients with ischemic HF may be more suitable candidates for high-risk cardiac surgery than nonischemic patients. Particularly isolated CABG may be safely performed even for patients who are considered high risk based on the current scoring system.

Limitations

This study was a retrospective cohort investigation with a small number of subjects; therefore, any conclusions are limited and are hypothesis generating. In the survival analyses, we used the date of first surgery as time zero instead of the date of decision, as we aimed to compare the surgical outcomes of each approach instead of overall outcomes. Thus, it is possible that we are underestimating the mortality of the VAD/transplant route because we did not include the waitlist mortality, which may augment the survival benefit of the conventional surgery strategy.

CONCLUSIONS

The outcomes of conventional cardiac surgery in highly selected patients with end-stage HF were acceptable and the long-term survival was comparable with the one after our advanced surgical therapies. Particularly for patients with an ischemic cardiomyopathy, strong consideration for conventional surgery should be given before offering advanced therapies such as transplantation or LVAD.

Conflict of Interest Statement

Dr McDonald reports personal fees from Novartis for work on their advisory board and clinical trials. Dr Rao reports personal fees for consulting work for St. Jude Medical.

All other authors have nothing to disclose with regard to commercial support.

References

1. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128:1810-52.
2. Colvin-Adams M, Smithy JM, Heubner BM, Skeans MA, Edwards LB, Waller C, et al. OPTN/SRTR 2012 Annual Data Report: heart. *Am J Transplant*. 2014;14:113-38.
3. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, et al. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med*. 2001;345:1435-43.
4. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med*. 2009;361:2241-51.
5. Owens AT, Jessup M. Should left ventricular assist device be standard of care for patients with refractory heart failure who are not transplantation candidates? Left ventricular assist devices should not be standard of care for transplantation-ineligible patients. *Circulation*. 2012;126:3088-94.
6. Allen LA, Stevenson LW, Grady KL, Goldstein NE, Matlock DD, Arnold RM, et al. Decision making in advanced heart failure: a scientific statement from the American Heart Association. *Circulation*. 2012;125:1928-52.
7. Kunadian V, Zaman A, Qiu W. Revascularization among patients with severe left ventricular dysfunction: a meta-analysis of observational studies. *Eur J Heart Fail*. 2011;13:773-84.
8. Bishay ES, McCarthy PM, Cosgrove DM, Hoercher KJ, Smedira NG, Mukherjee D, et al. Mitral valve surgery in patients with severe left ventricular dysfunction. *Eur J Cardiothorac Surg*. 2000;17:213-21.
9. Czer LSC, Goland S, Soukiasian HJ, Gallagher S, De Robertis MA, Mirocha J, et al. Aortic valve replacement or heart transplantation in patients with aortic stenosis and severe left ventricular dysfunction. *Transplant Proc*. 2013;45:364-8.
10. Bhudia SK, McCarthy PM, Kumpati GS, Helou J, Hoercher KJ, Rajeswaran J, et al. Improved outcomes after aortic valve surgery for chronic aortic regurgitation with severe left ventricular dysfunction. *J Am Coll Cardiol*. 2007;49:1465-71.
11. Ahmed WA, Tully PJ, Baker RA, Knight JL. Survival after isolated coronary artery bypass grafting in patients with severe left ventricular dysfunction. *Ann Thorac Surg*. 2009;87:1106-12.
12. Tarantini G, Buja P, Scognamiglio R, Razzolini R, Gerosa G, Isabella G, et al. Aortic valve replacement in severe aortic stenosis with left ventricular dysfunction: determinants of cardiac mortality and ventricular function recovery. *Eur J Cardiothorac Surg*. 2003;24:879-85.
13. Maltais S, Tchanchaleishvili V, Schaff HV, Daly RC, Suri RM, Dearani JA, et al. Management of severe ischemic cardiomyopathy: left ventricular assist device as destination therapy versus conventional bypass and mitral valve surgery. *J Thorac Cardiovasc Surg*. 2014;147:1246-50.
14. Halkos ME, Chen EP, Sarin EL, Kilgo P, Thourani VH, Lattouf OM, et al. Aortic valve replacement for aortic stenosis in patients with left ventricular dysfunction. *Ann Thorac Surg*. 2009;88:746-51.
15. Appoo J, Norris C, Merali S, Graham MM, Koshal A, Knudtson ML, et al. Long-term outcome of isolated coronary artery bypass surgery in patients with severe left ventricular dysfunction. *Circulation*. 2004;110:II13-7.
16. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119:e391-479.
17. Mehra MR, Kobashigawa J, Starling R, Russell S, Uber PA, Parameshwar J, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates—2006. *J Heart Lung Transplant*. 2006;25:1024-42.
18. Jegannathan R, Maganti M, Badiwala MV, Rao V. Concomitant mitral valve surgery in patients undergoing surgical ventricular reconstruction for ischaemic cardiomyopathy. *Eur J Cardiothorac Surg*. 2013;43:1000-5.
19. Jones RH, Velazquez EJ, Michler RE, Sopko G, Oh JK, O'Connor CM, et al. Coronary bypass surgery with or without surgical ventricular reconstruction. *N Engl J Med*. 2009;360:1705-17.
20. Witkowski TG, ten Brinke EA, Delgado V, Ng ACT, Bertini M, Marsan NA, et al. Surgical ventricular restoration for patients with ischemic heart failure: determinants of two-year survival. *Ann Thorac Surg*. 2011;91:491-8.
21. Society of Thoracic Surgeons. Adult cardiac surgery data collection—training manual v2.81. Available at: <http://www.sts.org/sts-national-database/database-managers/adult-cardiac-surgery-database/data-collection>. Accessed December 21, 2016.
22. Lund LH, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dipchand AI, et al. The Registry of the International Society for Heart and Lung Transplantation: thirty-first official adult heart transplant report-2014; focus theme: retransplantation. *J Heart Lung Transplant*. 2014;33:996-1008.
23. Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, et al. Sixth INTERMACS annual report: a 10,000-patient database. *J Heart Lung Transplant*. 2014;33:555-64.
24. Shahian DM, O'Brien SM, Filardo G, Ferraris VA, Haan CK, Rich JB, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 1—coronary artery bypass grafting surgery. *Ann Thorac Surg*. 2009;88:S2-22.
25. O'Brien SM, Shahian DM, Filardo G, Ferraris VA, Haan CK, Rich JB, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2—isolated valve surgery. *Ann Thorac Surg*. 2009;88:S23-42.
26. Shahian DM, O'Brien SM, Filardo G, Ferraris VA, Haan CK, Rich JB, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 3—valve plus coronary artery bypass grafting surgery. *Ann Thorac Surg*. 2009;88:S43-62.
27. Fedoruk LM, Tribble CG, Kern JA, Peeler BB, Kron IL. Predicting operative mortality after surgery for ischemic cardiomyopathy. *Ann Thorac Surg*. 2007;83:2029-35; discussion 2035.
28. Kainuma S, Taniguchi K, Daimon T, Sakaguchi T, Funatsu T, Miyagawa S, et al. Mitral valve repair for medically refractory functional mitral regurgitation in patients with end-stage renal disease and advanced heart failure. *Circulation*. 2012;126:S205-13.
29. Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med*. 2011;364:1607-16.
30. Fox KF, Cowie MR, Wood DA, Coats AJ, Gibbs JS, Underwood SR, et al. Coronary artery disease as the cause of incident heart failure in the population. *Eur Heart J*. 2001;22:228-36.
31. Stevenson LW, Tillisch JH, Hamilton M, Luu M, Chelmsky-Fallick C, Moriguchi J, et al. Importance of hemodynamic response to therapy in predicting survival with ejection fraction $\leq 20\%$ secondary to ischemic or nonischemic dilated cardiomyopathy. *Am J Cardiol*. 1990;66:1348-54.

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