Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness

The ESCAPE Trial

The ESCAPE Investigators and ESCAPE Study Coordinators*

Context Pulmonary artery catheters (PACs) have been used to guide therapy in multiple settings, but recent studies have raised concerns that PACs may lead to increased mortality in hospitalized patients.

Objective To determine whether PAC use is safe and improves clinical outcomes in patients hospitalized with severe symptomatic and recurrent heart failure.

Design, Setting, and Participants The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) was a randomized controlled trial of 433 patients at 26 sites conducted from January 18, 2000, to November 17, 2003. Patients were assigned to receive therapy guided by clinical assessment and a PAC or clinical assessment alone.The target in both groups was resolution of clinical congestion, with additional PAC targets of a pulmonary capillary wedge pressure of 15 mm Hg and a right atrial pressure of 8 mm Hg. Medications were not specified, but inotrope use was explicitly discouraged.

Main Outcome Measures The primary end point was days alive out of the hospital during the first 6 months, with secondary end points of exercise, quality of life, biochemical, and echocardiographic changes.

Results Severity of illness was reflected by the following values: average left ventricular ejection fraction, 19%; systolic blood pressure, 106 mm Hg; sodium level, 137 mEq/L; urea nitrogen, 35 mg/dL (12.40 mmol/L); and creatinine, 1.5 mg/dL (132.6 μmol/L). Therapy in both groups led to substantial reduction in symptoms, jugular venous pressure, and edema. Use of the PAC did not significantly affect the primary end point of days alive and out of the hospital during the first 6 months (133 days vs 135 days; hazard ratio [HR], 1.00 [95% confidence interval {CI}, 0.82-1.21]; $P=.99$), mortality (43 patients [10%] vs 38 patients [9%]; odds ratio [OR], 1.26 [95% CI, 0.78-2.03]; $P=.35$), or the number of days hospitalized (8.7 vs 8.3; HR, 1.04 [95% CI, 0.86-1.27]; $P=.67$). In-hospital adverse events were more common among patients in the PAC group (47 [21.9%] vs 25 [11.5%]; $P=.04$). There were no deaths related to PAC use, and no difference for in-hospital plus 30-day mortality (10 [4.7%] vs 11 [5.0%]; OR, 0.97 [95% CI, 0.38-2.22]; $P=.97$). Exercise and quality of life end points improved in both groups with a trend toward greater improvement with the PAC, which reached significance for the time trade-off at all time points after randomization.

Conclusions Therapy to reduce volume overload during hospitalization for heart failure led to marked improvement in signs and symptoms of elevated filling pressures with or without the PAC. Addition of the PAC to careful clinical assessment increased anticipated adverse events, but did not affect overall mortality and hospitalization. Future trials should test noninvasive assessments with specific treatment strategies that could be used to better tailor therapy for both survival time and survival quality as valued by patients.

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ADVANCES IN MEDICAL THERAPY have improved outcomes for many ambulatory patients with heart failure and low ejection fraction (EF).[1-4] However, each year an estimated 250 000 to 300 000 patients are hospitalized for heart failure with low EF,[5] and the 1-year survival rate after hospitalization may be as low as 50%, even with recommended medical therapies.[6,7]

In nonrandomized studies, patients undergoing therapy with vasodilators and diuretics to reduce filling pressures to near normal levels have had acute and sustained improvements in hemodynamics, mitral regurgitation, and exercise tolerance.[8-15] Without a randomized study of hemodynamic monitoring with the pulmonary artery catheter (PAC), however, it could not be determined whether PACs improved outcomes in addition to other components of intensive heart failure management.

There is considerable controversy over use of the PAC in critical illness. The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) trial demonstrated higher mortality for patients thought to require PAC during hospitalization, although without excess risk for patients with heart failure.[16] Reports from acute myocardial infarc-

See also pp 1664 and 1693.

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tion populations further raised concerns that PACs increased mortality, and a moratorium on PAC use was proposed.[17] Recommendations from a working group of representatives from the National Heart, Lung, and Blood Institute (NHLBI), the Food and Drug Administration, and academic experts in cardiology, pulmonology, surgery, nursing, and critical care led to a trial designed to test the PAC in patients with chronic heart failure.[18]

The complexity of this population and the challenge of hemodynamic measurement made experience in hemodynamic studies desirable. However, refinement of clinical assessment based on prior hemodynamic investigation could diminish the impact of PAC information. Recognizing this conflict,[18] the decision was made to test the PAC with experienced heart failure investigators. For the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE), the primary hypothesis was that for patients with severe heart failure, therapy guided by PAC monitoring and clinical assessment would lead to more days alive and fewer days hospitalized during 6 months compared with therapy guided by clinical assessment alone.

METHODS

Trial Organization

ESCAPE was an NHLBI-sponsored randomized trial conducted at 26 experienced heart failure centers in the United States and Canada. The Brigham and Women's Hospital served as the clinical coordinating center, and Duke Clinical Research Institute was the data coordinating center and performed all statistical analyses. The NHLBI appointed an independent data and safety monitoring board. Participating institutional review boards approved the protocol, and written informed consent was obtained from all patients.

Patients

Inclusion criteria were designed to select patients with severe symptomatic heart failure despite recommended therapies.[18] The target patient was sufficiently ill with advanced heart failure to make use of the PAC reasonable, but also sufficiently stable to make crossover to PAC for urgent management unlikely. Severity prior to admission could be met by the following criteria: (1) hospitalization for heart failure within the past year; (2) urgent visit to the emergency department; or (3) treatment during the preceding month with more than 160 mg of furosemide daily (or equivalent). Randomization required at least 3 months of symptoms despite angiotensin-converting enzyme (ACE) inhibitors and diuretics, left ventricular (LV) EF 30% or less, systolic blood pressure 125 mm Hg or less, and at least 1 sign and 1 symptom of congestion. Exclusion criteria to minimize confounding comorbidities or urgent crossover included creatinine level greater than 3.5 mg/dL (309.4 μmol/L), or prior use of dobutamine or dopamine more than 3 μg/kg/min, or any prior use of milrinone during the current hospitalization. Right heart catheterization to assess pulmonary hypertension during transplant evaluation was permitted in patients receiving therapy guided by clinical assessment alone if performed at the end of hospitalization.

A concurrent PAC registry was established to characterize hospitalized patients receiving PACs considered to be required during heart failure management.

Study Design and Analyses

Patients were randomly assigned 1:1 to therapy guided by clinical assessment only (clinical assessment group) or therapy guided by clinical assessment and the PAC (PAC group). Randomization was stratified by site using random block sizes of 2 or 4 through a central telephone center. The treatment goal in the clinical assessment group was resolution of clinical signs and symptoms of congestion, particularly jugular venous pressure elevation, edema, and orthopnea. Treatment goals in the PAC group were the same, with the addition of pulmonary capillary wedge pressure (PCWP) of 15 mm Hg and right atrial pressure of 8 mm Hg. Therapy was adjusted in both groups to avoid progressive renal dysfunction or symptomatic systemic hypotension.

The protocol did not specify drug selection or dosing. Investigators were encouraged to follow national guidelines for treatment of heart failure and to primarily use intravenous diuretics and vasodilators. The use of inotropic agents for routine management was consistently and explicitly discouraged. No specific instructions were given regarding nesiritide, which became available during the course of the trial.

The Pulmonary Artery Catheter Education Project, a computer-based program created by the NHLBI, the Food and Drug Administration, and the American College of Physicians, was used at study initiation to train investigators and coordinators (http://www.pacep.org/asahq). Catheters were selected according to individual institutional practice. In the PAC group, hemodynamics were measured twice at baseline and at least twice daily thereafter, with pressure measurement from paper readings. A specific case report form listed anticipated PAC complications.

Patients were seen at 7 to 14 days, and 1, 2, 3, and 6 months after discharge. Data were collected on clinical status, medications, exercise, and quality of life measurements. Race and ethnicity were assessed by the study coordinator from patients and chart information to determine degree of diverse representation in the study population. The primary end point, days alive out of the hospital during 6 months following randomization, was analyzed using the Cox proportional hazards model. Component end points included time to events. End points were calculated with patients receiving transplant or assist devices coded as dead, then recalculated coded as alive.

Because patients and physicians were not blinded to treatment, physiologic secondary end points, focusing on mitral regurgitation (the subject of pending analysis), natriuretic peptides, and peak oxygen consumption, were se-

lected as measurable without knowledge of group assignment. Other functional end points were 6-minute walk distance,[19] the Minnesota Living with Heart Failure questionnaire,[20] and the time trade-off tool,[21] which quantifies how many months of life out of 24 months patients would trade to feel better, through a series of binary questions asked by a trained coordinator, as has been described for moderate-severe heart failure. All baseline functional measures were made before randomization. A new end point of time trade-off–adjusted survival was prospectively defined for exploratory analysis as the integrated product of the days alive and the proportion of months preferred in current health at each time point.

The original design included 500 randomized patients, based on the assumption that the control group would have an expected 40 days dead or hospitalized with an SD of 30. The treated group was assumed to have an expected number of days of 32 (0.8×40). This resulted in an estimated power of 84%, assuming normality of days hospitalized (assuming a 2-sided test at an α level of .05). Interim unblinded analyses for efficacy occurred after 19%, 46%, 59%, and 67% of the patients had been enrolled. Approximate O'Brien-Fleming boundaries were used based on the group-sequential methods of Lan et al.[22] No provision was made for stopping early for futility. None of the tests were close to the stopping boundaries.

The secondary end points, including exercise, natriuretic peptides, and quality of life, were analyzed with the *t* test using SAS version 8.2 (SAS Institute Inc, Cary, NC) with an α level of .05. All analyses were based on intention to treat.

RESULTS

Baseline Characteristics

From January 18, 2000, to November 17, 2003, 433 patients were enrolled (FIGURE 1). The data and safety monitoring board recommended that the NHLBI stop the trial before enrolling 500 patients due to concerns of early adverse events and the unlikelihood of achieving a significant difference in the primary end point.

The 2 randomized groups had similar baseline characteristics (TABLE 1), with 391 (90%) taking ACE inhibitors or angiotensin-receptor blockers, 268 (62%) taking β-blockers, and 31 (7%) with implantable defibrillators. During the same time, patients receiving the PAC without randomization (PAC registry) had higher LVEF, but more compromise of blood pressure, serum sodium and creatinine levels, and inotropic therapy (35% vs 15%).

Treatment After Randomization

Intravenous diuretics were used in all patients. Vasodilator therapy was used in 80 (37%) patients in the PAC group and 42 patients (19%) in the clinical assessment group (total nesiritide, 66 [15%]; nitroprusside, 50 [12%]; nitroglycerin, 16 [4%]). Inotropic therapy was used in 94 (44%) patients in the PAC group and 86 patients (39%) in the clinical assessment group. Discharge prescriptions included ACE inhibitors/angiotensin-receptor blockers for 196 (91%) patients in the PAC group and 195 patients (89%) in the clinical assessment group, and β-blockers for 140 (65%) patients in the PAC group and 128 patients (59%) in the clinical assessment group.

PACs were placed for adjustment of therapy in 198 (92%) patients in the PAC group and 21 patients (10%) in the clinical assessment group during hospitalization. PACs in patients in the treatment group were in place for a median of 1.9 days, during which all hemodynamic parameters improved (TABLE 2). Substantial impact of therapy on clinical goals by the time of discharge was similar in both groups (TABLE 3). Although average weight loss was 3.2 kg for patients in the clinical assessment group vs 4.0 kg for patients in the PAC group, serum creatinine level worsened less often in the PAC group.

Primary End Point

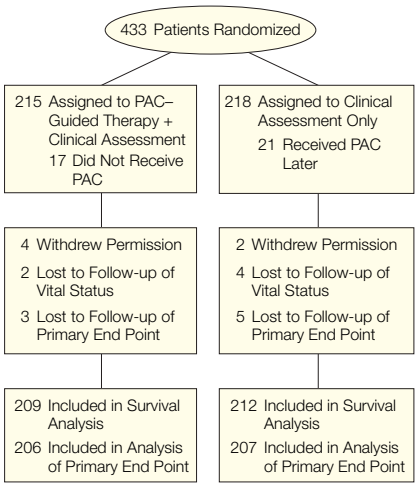
Use of the PAC did not affect the primary end point of days alive out of the hospital (FIGURE 2). The overall neutrality of the intervention was consistent across demographic subgroups (FIGURE 3). There were no significant differences in time to death or hospitalization, deaths, or days hospitalized (TABLE 4). Both groups had a median of 2.0 hospitalizations per patient. Coding the 36 patients who underwent cardiac transplantation or LV assist device placement as either dead or alive did not change the results.

There were no clinical subgroups in which benefit or harm was shown. There was a trend for better PAC outcomes in the centers with higher volume enrollment. There was no evidence of benefit or harm from the PAC in relation to intravenous vasoactive therapy (TABLE 5).

Safety of the PAC

Adverse events specifically attributed to PACs occurred in 9 patients in the PAC group and 1 patient in the clinical assessment group later receiving a PAC

Figure 1. CONSORT Diagram



CONSORT diagram depicting the progress of the 433 patients randomly assigned over the course of the trial and their contribution to the assessment of survival and the primary end point. Seventeen patients randomized to the pulmonary artery catheter (PAC) plus clinical assessment group did not receive a PAC due to logistic limitations of placement and subsequent monitoring. Patients randomized to the clinical assessment only group could receive an elective PAC as part of transplant evaluation, but all analyses were done based on original intention to treat.

Table 1. Baseline Characteristics of Randomized Patients and Patients Receiving Pulmonary Artery Catheterization (PAC) Without Randomization in ESCAPE Trial

Characteristic	PAC Group (n = 215)	Clinical Assessment Group (n = 218)	*P* Value, Clinical Assessment vs PAC*	PAC Registry (n = 439)	*P* Value, Randomized vs Registry†
Age, mean (SD), y	56 (14)	56 (14)	.82	59 (14)	<.001
Male, %	74	74	.93	69	.06
Race, No. (%)					
White	124 (58)	134 (62)	.42	348 (81)	<.001
Minority	91 (42)	84 (39)		80 (19)	
Etiology, No. (%)					
Ischemic	110 (51)	105 (49)	.60	240 (55)	.16
Nonischemic	105 (49)	113 (51)		199 (45)	
Heart rate, mean (SD), beats/min	83 (15)	82 (16)	.70	84 (18)	.67
Ejection fraction, mean (SD), %	19 (7)	20 (6)	.53	24 (14)	<.001
Systolic blood pressure, mean (SD), mm Hg	106 (17)	106 (15)	.77	104 (21)	.008
Sodium, mean (SD), mEq/L	137 (4.4) (n = 213)	137 (4.4) (n = 216)	.66	135 (5.3)	<.001
Urea nitrogen, mean (SD), mg/dL	34 (21)	36 (24)	.88	42 (30)	.004
Creatinine, mean (SD), mg/dL	1.5 (0.6) (n = 215)	1.5 (0.6) (n = 216)	.50	2.0 (1.5)	<.001
Baseline BNP, mean (SD), pg/mmol	974 (1216)	1018 (1400)	.96	NA	NA
Peak Vo_2, mean (SD)	10.2 (3.9) (n = 61)	9.9 (2.9) (n = 650)	.90	NA	NA
6-min walk, mean (SD), ft	390 (400) (n = 193)	437 (431) (n = 198)	.37	NA	NA
Baseline MLHF score, mean (SD)	74 (17)	73 (18)	.60	NA	NA

Abbreviations: BNP, brain natriuretic peptide; ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; MLHF, Minnesota Living with Heart Failure; NA, not applicable; VO_2, peak oxygen consumption.
SI conversion factors: To convert urea nitrogen to mmol/L, multiply by 0.357; creatinine to μmol/L, multiply by 88.4.
**P* value for comparison between PAC and clinical assessment groups.
†*P* value for comparison between ESCAPE trial and PAC registry.

Table 2. Impact of Therapy Guided by Pulmonary Artery Catheterization During the Course of Hospitalization*

Hemodynamic Measurement	Baseline	Final†
Right atrial pressure, mm Hg	14 (10)	10 (7)
Pulmonary capillary wedge pressure, mm Hg	25 (9)	17 (7)
Cardiac index, L/min/m^2	1.9 (0.6)	2.4 (0.7)
Cardiac output, L/min	3.8 (1.2)	4.8 (2.1)
Systemic vascular resistance, dynes × sec/cm^5	1500 (800)	1100 (500)

*Data are expressed as mean (SD).
†*P*<.001 for all variables. The final hemodynamics are those measured just before removal of the pulmonary artery catheter, which occurred at a median of 1.9 days after insertion.

(TABLE 6). These specific events were PAC-related infection (4 patients), bleeding (2 patients), catheter knotting (2 patients), pulmonary infarction/hemorrhage (2 patients), and ventricular tachycardia (1 patient). There were no hospital deaths attributed to the PAC. Adverse events, most commonly infection, occurred in-hospital almost twice as often in the PAC patients, but occurred in 143 patients in each group over 6 months. Other cardiac procedures occurred in 81 (38%) patients in the PAC group and 89 (41%) in the clinical assessment group during hospitalization.

Secondary End Points

Natriuretic peptides decreased similarly in both groups. Functional end points improved significantly during hospitalization in both groups, with a trend for more improvement in the PAC group (FIGURE 4). The Minnesota Living with Heart Failure questionnaire improved in both groups by 1 month, with greater improvement in the PAC group. By 6 months, scores in the clinical assessment group had improved to match the PAC group.

The time trade-off showed greater improvement for the PAC group compared with the clinical assessment group at all time points (1, 2, 3, and 6 months; *P*=.001-.02). By the end of the study, the average improvement (decrease in survival months to be traded for better health) was 6.2 months in the PAC group compared with 0.9 months in the clinical assessment group. Benefit remained if LV assist device or transplant patients were given the worst score (*P*=.03-.05). When the missing data were modeled using the newly described method of Davidian et al,[23] the results were no longer significant, but the effects trended in the same direction. The exploratory secondary end point of direct time trade-off–adjusted

Table 3. Impact of Interventions on Discharge Status*

	PAC Group (n = 215)			Clinical Assessment Group (n = 218)		
	Baseline	Discharge	Mean Change	Baseline	Discharge	Mean Change
Weight, kg	85.7 (21.8)	80.8 (20.3)	–4.0 (5.4)†	85.6 (20.3)	82.2 (20.4)	–3.4 (4.2)†
Systolic blood pressure, mm Hg	106 (17)	102 (15)	–4 (17)†	106 (15)	102 (15)	–4 (17)†
Estimated jugular venous pressure, mm Hg	12.1‡	6.7‡	45%†	12.5‡	7.3‡	42%†
Edema§	134 (67)	41 (20)	–93 (46)†	139 (68)	42 (21)	–97 (48)†
Creatinine, mg/dL‖	1.5 (0.6)	1.5 (0.6)	0.0 (0.4)	1.5 (0.6)	1.6 (0.9)	0.1 (0.8)†
Urea nitrogen, mg/dL	34 (21)	37 (21)	2 (18)	36 (24)	39 (23)	4 (21)†
Sodium, mEq/L	136.5 (4.4)	135.2 (3.9)	–1.3 (3.9)†	136.7 (4.4)	135.4 (4.6)	–1.4 (4.4)†
Symptom score (global)	43 (22)	68 (20)	25 (25)†	41 (21)	65 (20)	24 (24)†
Orthopnea (0-4 scale)	3.3 (1.1)	1.9 (1.0)	–1.4 (1.2)†	3.4 (1.0)	2.1 (1.1)	–1.2 (1.2)†

Abbreviation: PAC, pulmonary artery catheter.
SI conversion factors: To convert creatinine to μmol/L, multiply by 88.4; urea nitrogen to mmol/L, multiply by 0.357.
*Data are expressed as mean (SD) unless otherwise indicated.
†Significant ($P<.05$) change from baseline to discharge.
‡Indicates estimated geometric means assuming a grouped log normal distribution, all geometric SDs were 1.4.
§Edema refers to the number of patients with edema; change indicates the fraction improving from baseline to discharge.
‖Significant ($P<.05$) change between treatments.

survival was dominated by survival and was neutral.

COMMENT

The ESCAPE trial selected a population more severely compromised than any other NHLBI-sponsored trial of medical therapy in patients with heart failure. The addition of PAC monitoring to clinical assessment had no overall effect on the primary end point. Although there were more adverse events in-hospital associated with the PAC, there was no excess early mortality. There was a consistent trend for greater functional improvement after therapy guided by the PAC.

Neutral Impact of PAC on Primary End Point

The absence of benefit for the PAC on the primary end point could have resulted from multiple factors listed below, as anticipated in the original design.[18]

Safety

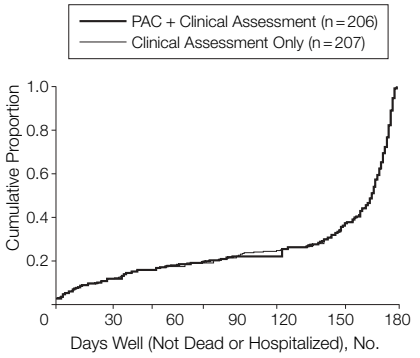
Previous retrospective studies raised the possibility that the catheter itself was associated with sufficient adverse events to influence major outcomes.[16,24,25] The PAC, as used by the investigating sites in ESCAPE, appeared overall to be safe. The results suggest that retrospective reports of excess mortality with PACs were confounded by the severity of clinical status leading to the decision to use PACs. This is supported by the more severe clinical compromise in PAC registry patients in this study (Table 1). In ESCAPE there were only 9 (4.2%) direct procedural complications, which may reflect both experienced sites and specific education prior to site enrollment.

Impact of Therapy to Reduce Filling Pressures

In the PAC group, therapy tailored to approach a PCWP of 15 mm Hg and a right atrial pressure of 8 mm Hg reduced these pressures effectively. Marked clinical resolution of the signs and symptoms of congestion occurred in both groups (Table 3), providing a benchmark for the effectiveness of therapy during hospitalization for heart failure. The accuracy of skilled investigators in clinical assessment of filling pressures may have been adequate to identify and monitor the clinical interventions required without precise hemodynamic confirmation.

The prognostic importance of achieving low PCWP at discharge has been previously described.[26-28] The relation between filling pressures and mortality likely reflects multiple interactions with disease progression.[29-31] As in prior experiences, it is not possible to determine whether achievement of lower filling pressures actually caused better outcomes or merely identified patients with more favorable outcomes regardless of therapy.

Figure 2. Cumulative Primary End Point (Days Alive and Out of Hospital)

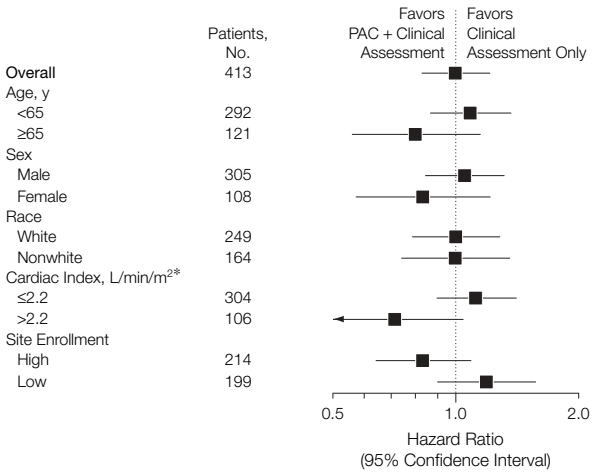


Cumulative proportion of patients contributing each possible numeric outcome for the number of days neither dead nor hospitalized during the 180 possible days of follow-up. Patients at the far left side of the curve represent early deaths, while those counted as 180 days survived for 6 months without rehospitalization. The curves for the treatment groups, pulmonary artery catheter (PAC) plus clinical assessment and clinical assessment only are superimposed.

Choice of Therapies

Benefit derived from the PAC might have been offset if knowing hemodynamic information triggered excess use of medications with deleterious consequences. Such differences appeared to

Figure 3. Impact of Intervention on Primary End Point Across Demographic Subgroups



The hazard ratio for the primary end point of days neither dead nor hospitalized is provided for subgroups based on prerandomization characteristics. A clinical estimate of whether the cardiac index was above or below 2.2 L/min/m^2 was part of the information required from the investigator prior to randomization. The centers were divided into the high and low enrolling sites based on the number of patients randomized. Complete data on mortality and rehospitalization were available for 413 patients who were used for analysis of the primary end point.
*Three patients did not have a clinical estimate of cardiac index recorded at the time of randomization.

Table 4. Primary Outcomes: Mortality and Hospitalizations

Measure	PAC Group	Clinical Assessment Group	End Point Estimate (95% CI)*	χ^2	*P* Value
Days alive out of hospital, mean					
LVADs/transplants coded dead	133	135	Hazard ratio, 1.00 (0.82-1.21)	0.00	.99
LVADs/transplants coded well	141	143	Hazard ratio, 0.99 (0.82-1.21)	0.00	.95
Mortality (dead at 180 d), No.	43	38	Odds ratio, 1.26 (0.78-2.03)	0.86	.35
Total days initial hospitalization, mean	8.7	8.3	Hazard ratio, 1.04 (0.86-1.27)	0.18	.67
PAC-related deaths, No.	0	0	NA	NA	NA
Early deaths (in-hospital plus 30 d), No.	10	11	Odds ratio, 0.97 (0.38-2.22)	0.04	.97

Abbreviations: CI, confidence interval; LVAD, left ventricular assist device; NA, not applicable; PAC, pulmonary artery catheter.
*Values less than 1 favor PAC.

Table 5. Primary End Point Results by Inotrope and Vasodilator Use After Randomization

Group	Event Rates, %*		Primary End Point Hazard Ratio (95% CI)	*P* Value
	PAC Group	Clinical Assessment Group		
Inotrope (n = 180)	72	73	0.93 (0.69-1.27)	.66
No inotrope (n = 253)	62	60	1.00 (0.78-1.29)	.97
Vasodilator without inotrope (n = 75)	66	57	0.99 (0.60-1.64)	.98
Neither inotrope or vasodilator (n = 178)	59	61	0.93 (0.68-1.27)	.63

Abbreviation: CI, confidence interval.
*Event rates are compared between PAC group and clinical assessment group for the 4 drug treatment groups. Event rates for the 4 groups by drug treatment are not compared, as the inotrope and vasodilator therapies were not selected by randomization.

result from PAC use following surgery.[32] Differences in use of intravenous vasoactive agents did occur in the ESCAPE study and may have affected mortality,[33] but there was no benefit of PAC use on the primary end point, even for patients who received neither intravenous inotropic nor vasodilator therapy (Table 5). The possibility remains that a potential benefit of hemodynamic information was obscured by variability in how therapies were adjusted in response.

Comparison With Previous Results in Advanced Heart Failure

There have been no previous randomized trials of therapy tailored during continuous hemodynamic monitoring in heart failure. Use of an indwelling PAC to adjust therapy in advanced heart failure was first described by Kovick et al[34] and subsequently by Pierpont[35] for vasodilator therapy in decompensated heart failure with high systemic vascular resistance. It became common to assess reversibility of secondary pulmonary hypertension during transplant evaluation, for which reduction of LV filling pressures is crucial. The approach of tailoring therapy to reduce filling pressures was then extended to improve clinical status for patients awaiting or ineligible for transplantation.[36] This approach, combined with intensive outpatient heart failure management, was associated with reduced hospitalizations, decreased clinical congestion, and improved exercise capacity.[14,37,38] Similar experiences elsewhere demonstrated recognition of clinically unappreciated volume overload and improved exercise capacity when therapy was adjusted using PAC information.[39]

The advanced heart failure population and therapies have evolved since these experiences. Decompensation was previously accompanied by severe vasoconstriction, such that aggressive vasodilation in addition to diuresis was required to reduce filling pressures.[15,40] Patients now have longer duration of heart failure and ACE inhibitor use prior to advanced symptoms, and many have

received β-blockers. The average systemic vascular resistance at baseline in ESCAPE was only 1500 dynes × s/cm^5, compared with over 1800 dynes × s/cm^5 in several previous experiences.[15] However, progression of renal dysfunction and diuretic resistance more commonly limits therapy than previously.[41,42] The average discharge furosemide equivalent was 180 mg, compared with less than 100 mg in earlier experiences.[14] Current therapy during hospitalization for heart failure now may focus less on high filling pressures with vasoconstriction and more on high filling pressures with renal dysfunction.

There have been 11 previous randomized trials of PACs in critical illness, in which the goals of therapy diverged from those described here for heart failure.[32,43-46] A meta-analysis of these trials, including ESCAPE, showed a hazard ratio of 1.00 for mortality and hospitalization.[47] The recently published PAC-Man trial of 1014 patients from varied practice settings in the United Kingdom also demonstrated no effect on major end points in the overall population or in the 11% of patients with heart failure.[48] These trials support the safety of PACs and the overall neutral effect, while highlighting the challenge of assessing a diagnostic tool without a consistent strategy of response with effective therapies.

Table 6. Adverse Events In-hospital

Adverse Event	No. (%) PAC Group (n = 215)	No. (%) Clinical Assessment Group (n = 218)	*P* Value*
Implantable cardioverter-defibrillator firing	5 (2.3)	1 (0.5)	.08
Cardiogenic shock	6 (0.5)	2 (0.9)	.12
Ischemia/angina	9 (4.2)	4 (1.8)	.13
PAC infection	4 (1.9)	0 (0.0)	.03
Myocardial infarction	0 (0.0)	1 (0.5)	.75
Stroke or transient ischemic attack	1 (0.5)	0 (0.0)	.75
Cardiac arrest	9 (4.2)	5 (2.3)	.23
Infection	27 (12.6)	20 (9.2)	.25
Patients with at least 1 adverse event	47 (21.9)	25 (11.5)	.04

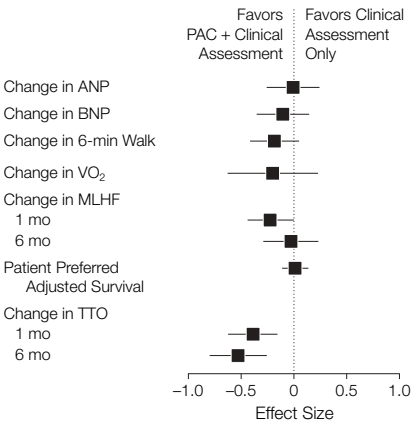
Abbreviation: PAC, pulmonary artery catheter.
**P* values calculated as Fisher exact mid-*P* values.

Secondary Functional End Points

Function and quality of life are crucial to patients with heart failure, a chronic debilitating disease. ESCAPE is distinct from other trials of PAC, which have included patients during acute events with anticipated complete recovery. As revealed in our patients' preferences, survival is not the only, and for some not the most important, metric of benefit. While improvement in clinical status in both groups was substantial and sustained, a consistent trend suggested greater improvement in patients in whom therapy had been adjusted using PACs. This could reflect the close relation between filling pressures and symptoms of congestion. Exercise capacity has been shown to improve with reduction of filling pressures beyond that needed to treat edema.[38,39] The heart failure questionnaire improvement was greater by 5 points at 1 month in the PAC group, a level that has been established as clinically meaningful to patients.[20,49]

The time trade-off tool has only recently been used to assess patients with heart failure.[21,50,51] Primarily used in severe illnesses such as cancer, it correlates with functional assessments and symptom scales, but with marked individual variation. Some patients want survival at any cost, while others focus more on improving daily life than prolonging it.[21] The improvement in the PAC group was more than twice as great at every time point, suggesting that the patients awarded more value to their lives after therapy adjusted to lower filling pressures. The time trade-off instrument has shown a strong relation between elevated jugular venous pressure and willingness to trade time for better health quality.[21] In ESCAPE, the average time to be traded out of 24 months was 9 months at the time of randomization, confirming that patients with this severity of illness place high value on improving their quality of life.

Figure 4. Change in Secondary End Points



Change in secondary end points is presented as an effect size of the changes in the 2 treatment groups. ANP indicates atrial natriuretic peptide; BNP, brain natriuretic peptide; VO_2, peak oxygen consumption; MLHF, Minnesota Living with Heart Failure questionnaire; and TTO, time trade-off score.

Applicability of ESCAPE Results

There were no subgroups identified in which the impact of PAC use was significantly different from the overall trial. The representation of 175 (40%) minority subjects and 112 (26%) women suggests that similar considerations apply to PAC use in these groups. The population was defined specifically to exclude patients in whom PAC insertion seemed likely for urgent management.

ESCAPE centers were specifically selected for experience with clinical and hemodynamic assessment during therapy for advanced heart failure. The ESCAPE benchmark for clinical improvement during hospitalization for heart failure derives from experienced clinicians, recognized to be more accurate with both physical assessment and interpretation of hemodynamic

measurements.[52] The safety of the PAC procedure also applies only to experienced centers, with a trend for better outcomes in those with the highest enrollment. With the absence of benefit for the primary end point, there is no rationale at this time to increase the number of centers using the PAC for the management of heart failure.

Limitations

Interpretation of the ESCAPE results is limited by the lack of definition of precise strategy in response to the hemodynamic information obtained. There was considerable variation between sites in use of medications. Exercise tests, quality of life questionnaires, and the time trade-off utility assessments were secondary end points, with missing data that could not be assumed to occur randomly. Challenge arises in interpreting positive findings among an array of secondary end points dominated by a neutral primary end point.

Implications for PAC Use in Advanced Heart Failure

Based on ESCAPE, there is no indication for routine use of PACs to adjust therapy during hospitalization for decompensation of chronic heart failure. It seems probable that there are some patients and some therapies that yield improved outcome with PAC monitoring and others with counterbalancing deleterious effects. The ESCAPE trial does not provide information on using PACs in cardiogenic shock or in triage for LV assist devices and cardiac transplantation.

For patients in whom signs and symptoms of congestion do not resolve with initial therapy, consideration of PAC monitoring at experienced sites appears reasonable if the information may guide further choices of therapy. In light of accumulating information regarding the deleterious effect of intravenous inotropic therapy, the PAC might be used to guide therapies for patients in whom inotropic therapy would otherwise be used.

The ESCAPE trial defined the most compromised patient population to be studied in an NHLBI heart failure trial with medical therapy, with 19% (83 patients) mortality at 6 months. No diagnostic test by itself will improve outcomes. New strategies should be developed to test both the interventions and the targets to which they should be tailored. Although most trials in a high-event population have focused on reducing mortality, patients with advanced heart failure express willingness to trade survival time for better health during the time remaining. How patients value their daily lives should help guide both the design and evaluation of new therapies.

Authors: Certifying authors are members of the Executive and Publications committees of the ESCAPE trial. Authors/members of the Executive and Publications committees, study investigators, and coordinators are listed below.

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Acquisition of data: Stevenson, O'Connor, Califf, Miller, Shah, Hasselblad, Francis, Leier, Binanay.
Analysis and interpretation of data: Stevenson, O'Connor, Califf, Sopko, Shah, Hasselblad, Francis.
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REFERENCES

1. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med*. 1991;325:303-310.
2. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325:293-302.
3. Pitt B, Zannad F, Remme WJ, et al; Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341:709-717.
4. Packer M, Coats AJ, Fowler MB, et al; Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344:1651-1658.
5. Fonarow GC, Adams KF, Abraham WT, Yancy CW, Boscardin WJ; ADHERE Scientific Advisory Committee, Study Group, and Investigators. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *JAMA*. 2005;293:572-580.
6. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *JAMA*. 2003;290:2581-2587.
7. Rose EA, Gelijns AC, Moskowitz AJ, et al; Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long-term mechanical left ventricular assistance for end-stage heart failure. *N Engl J Med*. 2001; 345:1435-1443.

8. Stevenson LW, Tillisch JH. Maintenance of cardiac output with normal filling pressures in patients with dilated heart failure. *Circulation*. 1986;74:1303-1308.
9. Stevenson LW, Brunken RC, Belil D, et al. Afterload reduction with vasodilators and diuretics decreases mitral regurgitation during upright exercise in advanced heart failure. *J Am Coll Cardiol*. 1990;15:174-180.
10. Stevenson LW, Sietsema K, Tillisch JH, et al. Exercise capacity for survivors of cardiac transplantation or sustained medical therapy for stable heart failure. *Circulation*. 1990;81:78-85.
11. Steimle AE, Stevenson LW, Chelimsky-Fallick C, et al. Sustained hemodynamic efficacy of therapy tailored to reduce filling pressures in survivors with advanced heart failure. *Circulation*. 1997;96:1165-1172.
12. Hamilton MA, Stevenson LW, Child JS, Moriguchi JD, Walden J, Woo M. Sustained reduction in valvular regurgitation and atrial volumes with tailored vasodilator therapy in advanced congestive heart failure secondary to dilated (ischemic or idiopathic) cardiomyopathy. *Am J Cardiol*. 1991;67:259-263.
13. Rosario LB, Stevenson LW, Solomon SD, Lee RT, Reimold SC. The mechanism of decrease in dynamic mitral regurgitation during heart failure treatment: importance of reduction in the regurgitant orifice size. *J Am Coll Cardiol*. 1998;32:1819-1824.
14. Fonarow GC, Stevenson LW, Walden JA, et al. Impact of a comprehensive heart failure management program on hospital readmission and functional status of patients with advanced heart failure. *J Am Coll Cardiol*. 1997;30:725-732.
15. Fonarow GC, Chelimsky-Fallick C, Stevenson LW, et al. Effect of direct vasodilation with hydralazine versus angiotensin-converting enzyme inhibition with captopril on mortality in advanced heart failure: the Hy-C trial. *J Am Coll Cardiol*. 1992;19:842-850.
16. Connors AF Jr, Speroff T, Dawson NV, et al; SUPPORT Investigators. The effectiveness of right heart catheterization in the initial care of critically ill patients. *JAMA*. 1996;276:889-897.
17. Dalen JE, Bone RC. Is it time to pull the pulmonary artery catheter? *JAMA*. 1996;276:916-918.
18. Shah MR, O'Connor CM, Sopko G, Hasselblad V, Califf RM, Stevenson LW. Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE): design and rationale. *Am Heart J*. 2001;141:528-535.
19. Bittner V, Weiner DH, Yusuf S, et al; SOLVD Investigators. Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. *JAMA*. 1993;270:1702-1707.
20. Rector TS, Tschumperlin LK, Kubo SH, et al. Use of the Living With Heart Failure questionnaire to ascertain patients' perspectives on improvement in quality of life versus risk of drug-induced death. *J Card Fail*. 1995;1:201-206.
21. Lewis EF, Johnson PA, Johnson W, Collins C, Griffin L, Stevenson LW. Preferences for quality of life or survival expressed by patients with heart failure. *J Heart Lung Transplant*. 2001;20:1016-1024.
22. Lan K, Gordon K, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika*. 1983;70:659-663.
23. Davidian M, Tsiatis A, Leon S. Semi-parametric estimation of treatment effect in a pretest-posttest study with missing data. *Stat Sci*. 2005;20:261-301.
24. Gore JM, Goldberg RJ, Spodick DH, Alpert JS, Dalen JE. A community-wide assessment of the use of pulmonary artery catheters in patients with acute myocardial infarction. *Chest*. 1987;92:721-727.
25. Zion MM, Balkin J, Rosenmann D, et al; SPRINT Study Group. Use of pulmonary artery catheters in patients with acute myocardial infarction: analysis of experience in 5,841 patients in the SPRINT Registry. *Chest*. 1990;98:1331-1335.
26. Stevenson LW, Tillisch JH, Hamilton M, et al. Importance of hemodynamic response to therapy in predicting survival with ejection fraction less than or equal to 20% secondary to ischemic or nonischemic dilated cardiomyopathy. *Am J Cardiol*. 1990;66:1348-1354.
27. Campana C, Gavazzi A, Berzuini C, et al. Predictors of prognosis in patients awaiting heart transplantation. *J Heart Lung Transplant*. 1993;12:756-765.
28. Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation*. 1997;95:2660-2667.
29. Kaye DM, Lambert GW, Lefkovits J, Morris M, Jennings G, Esler MD. Neurochemical evidence of cardiac sympathetic activation and increased central nervous system norepinephrine turnover in severe congestive heart failure. *J Am Coll Cardiol*. 1994;23:570-578.
30. Komuro I, Katoh Y, Kaida T, et al. Mechanical loading stimulates cell hypertrophy and specific gene expression in cultured rat cardiac myocytes: possible role of protein kinase C activation. *J Biol Chem*. 1991;266:1265-1268.
31. Leri A, Claudio PP, Li Q, et al. Stretch-mediated release of angiotensin II induces myocyte apoptosis by activating p53 that enhances the local renin-angiotensin system and decreases the Bcl-2-to-Bax protein ratio in the cell. *J Clin Invest*. 1998;101:1326-1342.
32. Sandham JD, Hull RD, Brant RF, et al; Canadian Critical Care Clinical Trials Group. A randomized controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med*. 2003;348:5-14.
33. Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. *JAMA*. 2005;293:1900-1905.
34. Kovick RB, Tillisch JH, Berens SC, Bramowitz AD, Shine KI. Vasodilator therapy for chronic left ventricular failure. *Circulation*. 1976;53:322-328.
35. Pierpont GL. Medical management of terminal cardiomyopathy. *J Heart Transplant*. 1982;2:18-27.
36. Stevenson LW, Dracup KA, Tillisch JH. Efficacy of medical therapy tailored for severe congestive heart failure in patients transferred for urgent cardiac transplantation. *Am J Cardiol*. 1989;63:461-464.
37. Lucas C, Johnson W, Hamilton MA, et al. Freedom from congestion predicts good survival despite previous class IV symptoms of heart failure. *Am Heart J*. 2000;140:840-847.
38. Stevenson LW, Steimle AE, Fonarow G, et al. Improvement in exercise capacity of candidates awaiting heart transplantation. *J Am Coll Cardiol*. 1995;25:163-170.
39. Chomsky DB, Lang CC, Rayos G, Wilson JR. Treatment of subclinical fluid retention in patients with symptomatic heart failure: effect on exercise performance. *J Heart Lung Transplant*. 1997;16:846-853.
40. Drazner MH, Hamilton MA, Fonarow G, Creaser J, Flavell C, Stevenson LW. Relationship between right and left-sided filling pressures in 1000 patients with advanced heart failure. *J Heart Lung Transplant*. 1999;18:1126-1132.
41. Weinfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. *Am Heart J*. 1999;138:285-290.
42. Butler J, Forman DE, Abraham WT, et al. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. *Am Heart J*. 2004;147:331-338.
43. Bender JS, Smith-Meek MA, Jones CE. Routine pulmonary artery catheterization does not reduce morbidity and mortality of elective vascular surgery: results of a prospective, randomized trial. *Ann Surg*. 1997;226:229-236.
44. Berlauk JF, Abrams JH, Gilmour IJ, O'Connor SR, Knighton DR, Cerra FB. Preoperative optimization of cardiovascular hemodynamics improves outcome in peripheral vascular surgery: a prospective, randomized clinical trial. *Ann Surg*. 1991;214:289-297.
45. Valentine RJ, Duke ML, Inman MH, et al. Effectiveness of pulmonary artery catheters in aortic surgery: a randomized trial. *J Vasc Surg*. 1998;27:203-211.
46. Bonazzi M, Gentile F, Biasi GM, et al. Impact of perioperative haemodynamic monitoring on cardiac morbidity after major vascular surgery in low risk patients: a randomised pilot trial. *Eur J Vasc Endovasc Surg*. 2002;23:445-451.
47. Shah MR, Stevenson LW, Binanay C, O'Connor CM, Sopko G, Califf RM. The impact of the pulmonary artery catheter on critically ill populations: a meta-analysis of randomized clinical trials. *JAMA*. In press.
48. Harvey S, Harrison DA, Singer M, et al. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. *Lancet*. 2005;366:472-477.
49. Abraham WT, Fisher WG, Smith AL, et al; MIRACLE Study Group. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. 2002;346:1845-1853.
50. Havranek EP, McGovern KM, Weinberger J, Brocato A, Lowes BD, Abraham WT. Patient preferences for heart failure treatment: utilities are valid measures of health-related quality of life in heart failure. *J Card Fail*. 1999;5:85-91.
51. Torrance GW. Measurement of health state utilities for economic appraisal: a review. *J Health Econ*. 1986;5:1-30.
52. Trottier SJ, Taylor RW. Physicians' attitudes toward and knowledge of the pulmonary artery catheter: Society of Critical Care Medicine membership survey. *New Horiz*. 1997;5:201-206.