Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE): Design and rationale

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Background There is little information about how to adjust pharmacologic agents in the treatment of patients with advanced congestive heart failure (CHF). Some studies have suggested that use of pulmonary artery catheterization to guide reductions in filling pressures may improve outcomes for patients with heart failure who are hospitalized with evidence of elevated filling pressures. However, there is no consensus regarding the true utility of this strategy. A randomized clinical trial is needed to test the safety, efficacy, and treatment benefit of pulmonary artery catheterization in patients with advanced CHF.

Study Design The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial is a multicenter, randomized trial designed to test the long-term safety and efficacy of treatment guided by hemodynamic monitoring and clinical assessment versus that guided by clinical assessment alone in patients hospitalized with New York Heart Association class IV CHF. Five hundred patients will be randomly assigned to receive either medical therapy guided by a combination of clinical assessment and hemodynamic monitoring (PAC arm) or medical therapy guided by clinical assessment alone (CLIN arm). The primary end point of ESCAPE will be the number of days that patients are hospitalized or die during the 6-month period after randomization. Secondary end points will include changes in mitral regurgitation, peak oxygen consumption, and natriuretic peptide levels. Other secondary end points will be pulmonary artery catheter–associated complications, resource utilization, quality of life measures, and patient preferences regarding survival.

Implications The primary goal of ESCAPE will be to provide information about the utility of the pulmonary artery catheter in patients with advanced heart failure, independent of various treatment approaches used by individual physicians. In addition, this study will define current outcomes for this severely compromised population. (Am Heart J 2001;141:528-35.)
In many situations, PAC use is surrounded by “clinical equipoise,” a condition for which there is no consensus within the clinical practice community regarding the true utility of an intervention. At a workshop conducted by the National Heart, Lung, and Blood Institute (NHLBI) and the US Food and Drug Administration (FDA), advanced heart failure was identified as an important disease state for which the workshop ultimately led to a clinical trial entitled the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE). In this article we describe the major challenges the investigators encountered in planning a trial of PAC in heart failure and the resulting design and rationale for the ESCAPE trial.

Background
Heart failure afflicts an estimated 4 to 5 million Americans, with approximately 400,000 new cases diagnosed each year. Advances in medical therapy have had an important impact on the symptoms and short-term survival of patients with moderate to severe heart failure. There has been only limited success, however, with pharmacologic agents in the approximately 250,000 to 350,000 patients with New York Heart Association (NYHA) class III or IV symptoms. Even when medical therapy has been optimized, the 2-year survival rate for patients with persistent class IV symptoms may be only 25%. Patients with NYHA class IV symptoms may benefit from the principles of care originally developed from experiences with cardiac transplant candidates. Hemodynamic monitoring to adjust therapy, often referred to as “tailored therapy,” is a central component of this care. The rationale for PAC-directed therapy is based on two theories: (1) that knowledge of the pulmonary capillary wedge pressure (PCWP), systemic vascular resistance (SVR), and their responses to therapy will lead to the most effective regimen that produces acute symptomatic improvement without excessive adverse effects and (2) that selection of medical regimens on the basis of these hemodynamic responses will lead to long-term benefit.

In nonrandomized studies patients receiving tailored therapy have had sustained improvements in hemodynamic parameters, reduction in severity of mitral regurgitation, improvement in exercise tolerance, and low 90-day hospital readmission rates. Without randomized trial data, however, uncertainty remains as to whether these findings represent a true treatment benefit, a “healthy survivor” effect or biased patient selection. The ESCAPE trial was designed to evaluate definitively a treatment strategy for heart failure that incorporates the use of PACs.

Methods

Study objectives
The primary objective of the ESCAPE trial is to evaluate the safety and efficacy of pulmonary artery catheterization in patients with decompensated heart failure. The primary hypothesis is that in patients with NYHA class IV symptoms therapy directed by invasive hemodynamic monitoring and clinical assessment (PAC arm) will lead to fewer deaths and hospital days during a 6-month period than will therapy guided by clinical assessment alone (CLIN arm).

ESCAPE will also determine the effect of therapy tailored to reduce filling pressures on mitral regurgitation, peak oxygen consumption, natriuretic peptides, and quality of life; define the relationship between these physiologic parameters and overall outcome; and evaluate cost and resource utilization associated with the PAC. Another objective includes determining the incidence and significance of PAC-related complications in academic institutions that have significant experience with hemodynamic monitoring. An additional objective is to assess the usefulness of measured physiologic parameters (e.g., natriuretic peptide levels) to serve as biomarkers for choosing effective therapies in patients with advanced heart failure.

Study population
The ESCAPE study will include 500 patients with NYHA class IV heart failure. Recruitment and enrollment will occur over 27 months. Investigators will identify patients with advanced heart failure who would be sufficiently ill so that use of a PAC would be appropriate but sufficiently stable so that management without the use of a PAC would also be considered reasonable. Because the ESCAPE protocol does not involve any investigational agents or techniques, patients will be eligible for dual randomization if they are on stable doses of investigational drugs.

Randomization and blinding. After providing informed consent, eligible patients will be randomized in a 1:1 ratio to either the PAC arm or the CLIN arm. Because the ESCAPE trial is not a blinded study, a number of substudies, assessed without knowledge of the randomization assignment, will be conducted. These substudies include an evaluation of changes in mitral regurgitation on echocardiography and an evaluation of changes in plasma atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and norepinephrine values.

Eligibility criteria. The entry criteria for ESCAPE (Table I) require patients to demonstrate at least one symptom of congestion, such as orthopnea, abdominal discomfort from hepatic congestion, severe fatigue with minimal exertion, or discomfort from edema or anasarca. In addition, patients must exhibit one sign of fluid overload that may include >10 cm of jugular venous distention, rales in more than one third of the lung fields, peripheral edema, hepatomegaly, or ascites.

Enrollment criteria will also include a left ventricular ejection fraction of <50% and at least one prior hospitalization for heart failure within the past year. Angiotensin-converting enzyme (ACE) inhibitors and diuretics must have been initiated or attempted at least 3 months before randomization. In addition, the systolic blood pressure should be ≤125 mm Hg to avoid enrollment of patients who are likely to respond to routine increases in vasodilators and diuretics.
Table I. Inclusion and exclusion criteria

Inclusion criteria
Patients eligible for the trial must comply with all the following at randomization:

1. Age ≥16 y
2. Current admission under the care of the heart-failure service at the site
3. Current admission for NTHFA class IV heart-failure symptoms
4. At least one prior admission for exacerbation of CHF within 12 months before randomization
5. Left ventricular ejection fraction <30% by contrast ventriculography, radionuclide ventriculography, or quantitative echocardiography within 1 year before randomization. The most recent measure of left-ventricular function should be used.
6. Documented history of heart failure for ≥3 mo
7. Attempted therapy with angiotensin-converting enzyme (ACE) inhibitors and diuretics for ≥3 mo before randomization
8. Systolic blood pressure ≤125 mm Hg
9. Elevated filling pressures, indicated by one symptom and one physical sign:
   Symptoms: Dyspnea at rest, in the supine position, or immediately on routine activity within one room; abdominal discomfort, severe anorexia, or nausea without apparent cause other than hepatosplanchic congestion
   Signs: Jugular venous pressure elevation >10 cm above the right atrium; square-wave Valsalva response; hepatomegaly, ascites, or edema in the absence of other obvious causes; rales greater than one third lung fields

Exclusion criteria

1. Acute decompensation that, according to the attending heart-failure physician, will likely require PAC insertion during the next 24 h
2. Inability to undergo PAC placement within the next 12 h
3. Active listing for cardiac transplantation
4. Present or anticipated mechanical ventilation
5. Present or anticipated mechanical circulatory assist device insertion, including intra-aortic balloon pumps and left ventricular assist devices
6. Any administration of intravenous milrinone within the previous 48 h
7. Current administration of intravenous dopamine or dobutamine at >3 µg/kg/min or dopamine or dobutamine administration for >24 h before randomization
8. Acute MI or cardiac surgery within the last 6 wk
9. Current admission for an acute coronary syndrome, including acute MI or unstable angina
10. Documented moderate to severe mitral or aortic stenosis
11. Anticipated revascularization procedure during the admission
12. Other planned surgical procedure during the admission
13. Documented primary pulmonary hypertension
14. Pulmonary infarction within the past month
15. Current pneumothorax
16. Current serum creatinine >3.5 mg/dL
17. Temperature >37.8°C
18. White blood cell count >13,000/mm³
19. Exacerbation of CHF because of a primary factor requiring specific therapy, such as severe anemia, clinical hypothyroidism, or active systemic infection
20. Presence of any noncardiac disease, such as cancer, likely to shorten life expectancy to <1 y
21. Inability to return to the site’s CHF program at 14 ± 7 d, 30 ± 14 d, 60 ± 14 d, 90 ± 14 d, and 180 ± 14 d after randomization
22. Pregnancy or lactation or child-bearing potential in the absence of contraception by oral contraceptives, an intrauterine device, or surgical sterilization. All women of child-bearing potential must have a negative pregnancy test before randomization.
23. Estimated large volume reservoir (major ascites or anasarca) thought to require extensive diuresis (>48 h) before major adjustment of other medications such as vasodilators
24. Temporary inability to place and monitor PAC, because of either patient factors such as excessive anticoagulation or to logistic factors such as temporary lack of bedside monitoring equipment

The trial excludes patients with severe cardiac decompensation that requires urgent PAC insertion in the judgment of the attending physicians. Patients with conditions that may lead to a perceived need for PAC insertion will be excluded, as well as those who have received milrinone within 48 hours before randomization or dopamine or dobutamine at ≥3 µg/kg/min or within 24 hours before randomization. Patients with a serum creatinine of ≥3.5 mg/dL will also be excluded. To avoid enrolling patients with rapidly reversible components of illness, patients with recent MI, mechanical ventilation, or temperature ≥37.8°C will be excluded. Finally, patients in whom a PAC cannot be inserted for technical reasons and those who are unable to return for follow-up visits will be excluded.

Treatment strategies

In the PAC arm therapeutic recommendations will be based on a combination of hemodynamic data and clinical findings. This trial will address whether the increased precision of hemodynamic assessment leads to a better outcome than treatment decisions in the CLIN arm, which will be guided primarily by physical signs and symptoms.

In the PAC arm, the goal is to reduce left ventricular filling pressures to reach a PCWP ≤15 mm Hg and a right atrial pressure ≤8 mm Hg. To achieve these goals, investigators are encouraged to reduce SVR to normal levels without producing symptomatic hypotension. Blood pressure or SVR limits have not been specified because patients become symptomatic at different levels. In the CLIN arm medications will be adjusted
until both the symptoms and signs of congestion have resolved.

In both arms, medications will be further adjusted as necessary until the following specific goals have been achieved: absence of physical signs indicating elevated intracardiac filling pressures, evidence of adequate peripheral perfusion, and serum creatinine ≤3.0 mg/dL. Therapy may be adjusted for evidence of postural hypotension. Both groups will receive medications recommended in published guidelines for the advanced heart failure population.27-30 Patients may receive any of the standard therapies for heart failure, regardless of their treatment group.

Discharge criteria include ≥24 hours on oral medications without a major change in diuretic or vasodilator doses, ≥24 hours without positive inotropic agents, and stable fluid balance as demonstrated by achievement of a specific dry weight on oral diuretics. In addition, before discharge patients will receive instructions about follow-up appointments, diet, exercise, preventive care, and flexible diuretic regimens. After discharge, patients will return to the heart failure clinic for routine evaluation at 7 to 14 days, 1 month, 2 months, 3 months, and 6 months.

Crossovers. Patients randomized to the CLIN arm may cross over to the PAC arm at any time if hemodynamic monitoring becomes necessary. Criteria for possible crossover from the CLIN arm to the PAC arm include progressive hemodynamic decompensation leading to the need for high-dose inotropic or mechanical support; inability to wean from intravenous inotropic agents; and progressive, oliguric renal insufficiency. Other indications for crossover include refractory symptomatic hypotension, worsening pulmonary edema, and diagnostic uncertainty of the primary process causing decompensation. In the case of crossover, the site clinician will contact a study-designated cardiologist who will document the reason for change in the assigned treatment strategy.

End points

The primary end point of the ESCAPE trial will be the number of days that patients are hospitalized or die during the 6-month period after randomization (Table II). The primary end point is a continuous measure that includes the most clinically relevant events in the advanced heart failure population. The investigators estimate that patients enrolled in the trial will have an average of two hospital admissions and an estimated mortality rate of 35% during the 6-month follow-up period.

The secondary end points will include time to rehospitalization or death during the 6-month follow-up period and time to death alone. Physiologic parameters, such as changes in mitral regurgitation, natriuretic peptide levels, peak oxygen consumption, and 6-minute walk distance will also be used as secondary end points. Other secondary end points will be resource and cost utilization, quality of life as measured by the Minnesota Living with Heart Failure Score and Time Trade-off Assessment, and PAC-associated complications. The secondary end point will also include two clinical performance measurements: the frequency of concordance between estimates of hemodynamics made by physicians with actual hemodynamic measurements and the correlation between estimates of death and rehospitalization made by all clinicians with actual death and rehospitalization rates.

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<td><strong>Primary end points</strong></td>
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<td>(PAC arm only) Frequency of concordance of measured hemodynamics within range estimated by physician investigator</td>
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<td>Predictive value of rehospitalization estimates made by physician investigator at time of randomization, discharge, and 1 mo</td>
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<td>Predictive value of rehospitalization estimates made by nurse investigator at time of randomization, discharge, and 1 mo</td>
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**Statistical analysis**

All analyses, except those of PAC-related complications, will use the intention-to-treat principle. An overall α of .05 will be used for the primary hypothesis. We will use the Cox proportional hazards model to assess whether there is a statistical difference between the two treatment arms.31,32 The statistical significance of interim treatment differences will be assessed by use of the group-sequential methods of Lan and DeMets.33 This approach will incorporate a spending function with an upper boundary that approximates the O’Brien-Fleming boundary.34 Cardiac transplants. A small percentage of ESCAPE patients may undergo cardiac transplantation during the study. Rather than censoring these data, two separate computations will be done in the statistical analysis for this group. In the first method, patients who undergo transplantation will be regarded as having reached the end point of death on the day of the transplantation. The number of hospital days they have accumulated to the point of transplantation will be used, along with the date of transplantation as the components of the primary end point. In the second method, the primary end point will be calculated as the number of days of hospitalization during the 6-month follow-up period and the actual date of death, if it occurs. The overall analyses of the primary end point will then be compared by use of these different computations for patients who undergo transplantation. Because of number of transplant patients is expected to be very small, there will likely be no significant difference in the results of the overall primary and secondary end points with either method.

**Organizational structure**

The organization of ESCAPE includes (1) a steering committee, (2) an executive committee, (3) an operations committee, (4) a clinical coordinators council, and (5) the Data Safety and Monitoring Board (DSMB).
(Figure 1). The steering committee is responsible for the overall scientific direction of the trial and consists of the site investigators, the executive committee, and the core laboratories. The site investigators represent a consortium of 39 academic physicians from 26 US and Canadian sites. The executive committee consists of a central group of steering committee members who will assess trial progress and address scientific, policy, and operational issues that do not require full steering committee review. The coordinators council, which consists of study coordinators from all the clinical sites, will review trial-related nursing issues.

An independent DSMB, appointed by the NHLBI, is responsible for ongoing review of patient safety. In addition, the DSMB will review and interpret emerging study data at preplanned interim analyses and provide recommendations to the executive committee about any necessary modifications of the protocol or termination of the study.

**Hemodynamic data collection**

Another goal of ESCAPE is to standardize hemodynamic data collection across the participating sites. The ESCAPE investigators have implemented a PAC education program (PACEP) created by the Pulmonary Artery Catheterization and Clinical Outcomes Committee, a working group composed of representatives from the NHLBI, the FDA, and critical care subspecialties. By using the PACEP module, the ESCAPE investigators will be able to describe an experience implementing uniform guidelines for the collection and interpretation of hemodynamic data. Ultimately, the goal is to create national standards for PAC use.

**Discussion**

Despite the scientific value of PACs, observational studies have indicated that these devices may actually increase morbidity and mortality. The ESCAPE trial will provide critical information on the use of PACs in the heart failure population by testing the hypothesis that treatment guided by PAC monitoring will lead to better outcomes than those achieved through clinical assessment alone. However, like other recent trials of therapies in this uniquely compromised population, ESCAPE will only test the hypothesis about PACs in patients for whom there is clinical equipoise. Extrapolation of the data to all patients with advanced heart failure will require knowledge of the denominator of patients in whom clinicians feel the PAC is essential for management.

A positive result for ESCAPE may reflect several important benefits. If achieving and maintaining near-normal filling pressures is indeed beneficial, then the PAC-based strategy may lead to better outcomes because investigators are able to identify high filling pressures more accurately with the device than with clinical assessment alone. The PAC also allows physicians to evaluate the hemodynamic response to drugs during titration of therapy—information that may help refine combinations of drugs and maintain lower filling pressure over longer periods. With knowledge of the PCWP, SVR, and other parameters, investigators may be able to titrate ACE inhibitors to higher doses than would have otherwise been achieved. It may also be possible to avoid excessive vasodilation in sensitive individuals that could contribute to neurohormonal activation and renal dysfunction.

There are also many potential reasons why the
ESCAPE trial may be negative. There may be a higher incidence of major PAC complications such as infection, pneumothorax, and pulmonary hemorrhage than previously reported. Factors influencing hemodynamics during the long term may be more important than the hemodynamic status at discharge. Clinicians may react to measured hemodynamics by increasing the use of agents that may have a deleterious impact on outcomes. Finally, physicians with extensive experience in heart failure management may use information from the history and physical examination so effectively that pulmonary artery catheterization is unnecessary.

The ultimate goal of the ESCAPE trial is to provide information that can be generalized to all patients with advanced heart failure, regardless of the specific therapeutic approaches used by individual physicians. The ESCAPE trial does not specify concomitant medications for either arm of the study because of the paucity of clinical trial data regarding the safety and efficacy of specific therapies for advanced heart failure. In addition, the array of strategies for the management of NYHA class IV heart failure varies according to institution and physician experience. For these reasons, standard protocols for the use of inotropic agents, diuretics, and vasodilators such as nitroprusside and nitroglycerin were not specified.

Use of inotrope therapy is believed by some investigators to represent a qualitatively different approach to the treatment of advanced heart failure. If so, randomization of patients treated with these agents would introduce a distinctly different group into ESCAPE and alter the potential interpretation of the trial results. The following rationale was offered for the decision to limit restrictions on the use and duration of inotropic agents. Most of the ESCAPE investigators believed that inotropic therapy was just one of many potential therapeutic options for patients with advanced heart failure and that low-dose inotropic therapy did not compromise the basic premise of the trial. Also, by allowing investigators to select inotropic agents as they would in clinical practice, the results of the trial would better reflect routine patient care and the effects of pulmonary artery catheterization in a broad population of patients with advanced heart failure.

Crossovers

Crossover patients present a unique challenge because all results will be analyzed by use of the intention-to-treat principle. A certain number of crossovers from the CLIN group to the PAC group are expected when treatment responses are not adequate. Such resistance to therapy will help to confirm that the trial has recruited true NYHA class IV heart failure patients. Although there are many valid reasons for crossover, a high crossover rate would dilute the apparent impact of the PAC.

The entry criteria clearly discourage enrollment of patients with a high likelihood of crossover to PAC (eg, those with high inotropic support, acute coronary syndromes, marked renal insufficiency, and assisted ventilation). The protocol offers clinicians latitude in selecting therapies for heart failure; therefore physicians may explore various treatment approaches before pursuing crossover to the PAC. Finally, the ESCAPE trial requires investigators to contact the clinical coordinating center to discuss alternative therapeutic plans before crossover. This approach should minimize the number of crossovers and provide a better understanding of why changes in treatment strategies occur.

Recruitment of women and minorities

One step to ensure wide applicability of study results in ESCAPE is the anticipated recruitment of at least 30% women and 30% racial and ethnic minorities. Inclusion of these groups will enhance the scientific validity of ESCAPE and provide insight into the unique features of advanced heart failure in these subgroups. This information may be a launching point for further prospective studies.

Conclusion

An impressive storehouse of clinical trial data exists in the areas of acute coronary syndromes and chronic heart failure, yet there is still a paucity of information available with regard to management of severely ill patients. A clinical strategy, rather than a single agent, will be tested in the ESCAPE trial. A focus on clinically relevant outcomes may translate to improved patient care. Ultimately, by addressing a critical question about PACs and challenging assumptions about current practice, the ESCAPE study may become a paradigm for future trials in the field of advanced heart failure.

References

28. Committee on Evaluation and Management of Heart Failure. Guide-
UCLA Cardiomyopathy Center/Division of Cardiology; Gary Francis, MD, Cleveland Clinic Foundation; Robert P. Frantz, MD, Mayo Clinic; Mihai Gheorghiade, MD, Northwestern Medical School; Michelle Hamilton, MD, Ahmanson-UCLA Cardiomyopathy Center/Division of Cardiology; Joshua Hare, MD, Johns Hopkins Hospital; James Hill, MD, University of Florida; Maryl Johnson, MD, Northwestern Medical School; Walter Kao, MD, Rush-Presbyterian-St Luke’s Medical Center; Edward K. Kasper, MD, Johns Hopkins Hospital; Todd Koelling, University of Michigan; Carl V. Leier, MD, Ohio State University Medical Center (cochair, Publications Committee); Leslie Miller, MD, University of Minnesota/Cardiovascular Division; Daniel F. Pauly, University of Florida; Ileana Pina, MD, University Hospitals of Cleveland; Barry K. Rayburn, MD, University of Alabama at Birmingham; Stuart D. Russell, MD, Duke University Medical Center; Heather Ross, MD, University of Toronto; Melvin J. Tonkon, MD, Anaheim Heart and Research Institute; Guillermo Torre, MD, Baylor College of Medicine; Lynne Wagoner, MD, University of Cincinnati; J. Wayne Wannica, Foothills Provincial General Hospital; John Wilson, MD, Vanderbilt Heart Failure Program; Clyde W. Yancy, MD, University of Texas Southwestern Medical Center; James B. Young, MD, Cleveland Clinic Foundation.

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