# Technology Assessment



**Technology Assessment Program**

# Evaluation of the Evidence on Benefits and Harms of Pulmonary Artery Catheter Use in Critical Care Settings

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**Agency for Healthcare Research and Quality**
**540 Gaither Road**
**Rockville, Maryland 20850**

# Evaluation of the Evidence on Benefits and Harms of Pulmonary Artery Catheter Use in Critical Care Settings

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None of the investigators has any affiliations or financial involvement related to the material presented in this report.

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# Chapter 1. Introduction

The Center for Medicare & Medicaid Services (CMS) requested that the Tufts Medical Center Evidence-based Practice Center (Tufts EPC) conduct a technology assessment report on pulmonary artery catheter (PAC) monitoring in patients hospitalized in critical care settings. The primary goal of the report is to describe the utility of PAC monitoring with relevance to the relative effect and safety of PAC monitoring and how it affects outcomes in the Medicare population (i.e., people at least 65 years old) hospitalized in critical care settings.

The specific questions addressed are described at the end of the Introduction. Below is a narrative review of PAC monitoring and other devices or techniques that are currently used to assess cardiac output and volume status in critical care settings.

## Pulmonary artery catheter description

The PAC, also widely known as a Swan-Ganz catheter, is a flow-directed balloon flotation catheter introduced in the 1970s (1). Pulmonary artery catheterization has steadily evolved into a frequently employed method of bedside monitoring of cardiac output and volume status that does not yet have a suitable alternative for continually evaluating hemodynamic status (2). Although initially PAC was introduced in cardiac care units, it has frequently been used in a wide range of critical care settings because of its ability to assess hemodynamic status that can aid in disease diagnosis and guide fluid and therapeutic drug management in critically ill patients.

PAC measures cardiac output and pressures in the superior vena cava, right heart, and pulmonary artery. Left ventricular filling pressure can also be estimated by measuring pulmonary artery occlusive pressure (PAOP). In addition, modern catheters can evaluate cardiovascular hemodynamics and status, including mixed venous oxygen saturation, and right ventricular end-diastolic volume and right ventricular ejection fraction. These measurements are commonly used to evaluate critically ill patients' hemodynamic status, complementing clinical assessment and guiding therapy.

### Catheterization and measurement techniques

PAC is a multi-lumen plastic catheter, 110 to 150 cm long with a balloon located just proximal to the tip of the distal lumen. In the majority of catheters a thermistor, which measures temperature changes for the assessment of cardiac output, is located proximal to the balloon. Two additional lumens (right ventricular port and venous infusion port, if present) located at 19 cm and 30 cm from the tip reach the right ventricle and right atrium or superior vena cava. The PAC is connected to the monitoring equipment through a semi-rigid, noncompliant fluid-filled tube and pressure transducer. The movements in the transducer membrane generate electrical impulses that are amplified and transmitted to a monitor.

The PAC is usually inserted percutaneously through an introducer sheath into a major vein (jugular, subclavian, or femoral) . It can also be inserted via a cut-down to the vein without an introducer. After insertion through the sheath, the balloon is slowly inflated with 1.5 cc of air and the catheter is floated through right side of the heart until it wedges in a branch of the pulmonary artery. The balloon is deflated and left in the pulmonary artery. The central pressures measured are PAOP, an indicator of left atrial pressure, the pulmonary artery pressure, the right atrial pressure, and the right ventricular pressure. The thermodilution technique allows cardiac output

determination through infusion of cold saline into the right atrial lumen that mixes with blood. The resultant temperature changes are recorded by the thermistor at the tip of the catheter. Cardiac output allows estimation of stroke volume, a measure of cardiac performance. In addition, other measurements that can be provided by the PAC include mixed venous oxygen saturation and oxygen saturations in the right heart chambers, which can be used to assess for the presence of an intracardiac shunt, right atrial pressures and PAOP, which can be used to assess cardiac valve dysfunction. The systemic vascular resistance and pulmonary vascular resistance can also be calculated from other hemodynamic variables. In summary, PAC provides a comprehensive assessment of cardiovascular function.

### Pulmonary artery catheter uses

PAC is used as a diagnostic tool for the following conditions (among others): sepsis and septic shock; pulmonary edema; primary pulmonary hypertension; valvular disease; intracardiac shunts; cardiac tamponade; and pulmonary embolus. In addition to initial assessment of hemodynamic function, PAC can be kept in place for several days allowing evaluation of serial measurements to monitor hemodynamic status. It is thus used to monitor the following conditions (among others): acute myocardial infarction complicated by cardiogenic shock, right ventricular infarction, ventricular septal defect, or papillary muscle rupture; cardiac surgery and post-operative recovery; trauma complicated by multiorgan failure; major thermal injury; and assessment of response to fluid and vasodilator therapies.

## Potential clinical value and harms

### Potential clinical value

Soon after its introduction, PAC use in intensive care settings disseminated prior to rigorous evaluation of the effect of its use on clinical outcomes or cost savings. The ability of PAC to provide a wide range of variables that are used to assess hemodynamic status and to guide therapy is seen as beneficial in the intensive care setting. A systematic review in 1996 by Cooper et al. evaluated 34 randomized and nonrandomized studies and found that they were evenly split among those that found no benefit or worse outcomes with PAC and those showing benefit (3). Subsequent randomized trials and a large risk-adjusted nonrandomized study in the late 1990s came to differing conclusions regarding the value and safety of PAC in intensive care settings (4-7). In response, the Society of Critical Care Medicine convened a Consensus Conference (of clinical specialists), which stated that the published evidence on PAC was poor; however, there was a recommendation against a moratorium on PAC use, although the need for clinical trials was highlighted (8;9). Subsequent studies and opinion pieces have further cast doubt on the value of PAC (10-12). Dalen called for a moratorium on the use of PAC for routine monitoring of patients undergoing major surgery and in patients with acute myocardial infarction; he also called for randomized controlled trials to demonstrate their benefit (10). Additionally in 1997, National Heart Lung and Blood Institute (NHLBI) and Food and Drug Administration (FDA) convened a Pulmonary Artery Catheterization and Clinical Outcomes (PACCO) Workshop to develop a criteria for insertion of PAC (13). The proceedings of the workshop was published as a consensus statement that highlighted many areas in which the data were insufficient and this directly led to NHLBI funding for two of the important randomized trials (14;15).

In addition to the questionable clinical value of PAC in the controlled study setting, a common concern is that adequately measuring hemodynamic data is fraught with difficulties. Examples include errors in positioning the PAC such that alveolar rather than pulmonary venous pressure is measured, confounding of readings from positive pressure ventilation, and failure of PAOP to accurately measure left ventricular preload and other measures (12). The data obtained from PAC has to be accurately interpreted and acted upon.

Recent guidelines reflect a shift in recommendations. Both the 2002 ACC/AHA Guideline Update on Perioperative Cardiovascular Evaluation for Noncardiac Surgery and the 2003 American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization recommend against the routine use of PAC for perioperative care, but do recommend its use in various settings (16;17). The 2003 guidelines state that "the appropriateness of routine PAC depends on the combination of risks associated with the (a) patient, (b) surgery, and (c) practice setting (the latter referring to the risks from PAC introduced by practice conditions and staff circumstances)" (17).

Two recent systematic reviews of PAC in the ICU setting both came to similar conclusions (18;19). The reviews evaluated 11 and 13 overlapping randomized trials of PAC or no PAC use. Both found nearly identical odds of death regardless of intervention and no clinically or statistically significant difference in length of hospital stay. One review noted that PAC was associated with higher overall hospital costs in four US studies (18). The other found higher use of inotropes and intravenous vasodilators with PAC use (19).

PAC is a complex diagnostic test. Like any diagnostic test, it will only make a difference if the diagnostic information leads to a therapeutic strategy that can improve outcomes. Thus, the current results (and thus lack of need for use) may reflect the fact that there are no proven effective therapies for the acute heart failure. While the benefits of diuretics, is currently under-evaluated in terms of dosing and duration, etc, other therapies (ACE inhibitors, beta blockers) have chronic effects that are beneficial with little known about how to optimize their acute effects. In terms of technology evaluation of PAC use this is an important issue for two reasons: 1) new therapies for acute heart failure are under development; 2) new much less invasive or indwelling methods of measuring cardiac and pulmonary pressures are being introduced into the clinical setting.

However, it is useful to consider where current knowledge about the value of PAC fits in Dennis Fryback's and John Thornbury's hierarchical model of the efficacy of diagnostic testing (20). Very briefly, their model includes 6 levels of efficacy, or benefit to patients and society, that can be used to assess diagnostic tests. The levels include

1. Technical efficacy: whether the test does what it claims (e.g., measures volume status)
2. Diagnostic accuracy efficacy: how often the test is correct (e.g., sensitivity and specificity)
3. Diagnostic thinking efficacy: whether the test is judged helpful in making a diagnosis
4. Therapeutic efficacy: whether the test is judged helpful in planning management
5. Patient outcome efficacy: whether patients clinically improve after the test compared with not having the test
6. Societal efficacy: cost-effectiveness or cost-benefit analyses from the societal perspective.

When evaluating the potential clinical value of a test, it is helpful to consider the level of efficacy being considered. Depending on the test under consideration, and the value to the patients of knowing their diagnosis or of altering management, different levels of efficacy may be

important. The use of PAC in an intensive care setting, after the first set of readings, primarily are used to plan management (level 4) with the expectation that this will improve patient outcomes by increasing the use of appropriate treatments (level 5).

### Potential harms

As an invasive procedure into the cardiopulmonary system, PAC is associated with potentially catastrophic adverse events. These will be discussed further under Question 4 regarding complications and adverse events. Broadly, the adverse events due to PAC can be categorized into those due to the invasive procedure, including hemorrhage, organ rupture, and loss of the guidewire; due to the pressure measurement techniques, including valvular and vascular damage, arrhythmias, and pulmonary injury; and due to the loss of skin integrity, including bleeding and infection. As described below, death, major morbidity (medical complications), and need for emergency major surgery are known risks.

## Key Questions

CMS requested a description of PAC and related devices, their indications, and a current systematic review of the evidence supporting their use. Specifically, they posed four questions for review, as follows.

**Question 1:** What types of devices and techniques are currently used to assess cardiac output and manage volume status in critical care settings (including operating and recovery rooms)?

**Question 2:** What are the specific indications for pulmonary artery catheter placement in critical care settings?

**Question 3:** Does therapeutic management of cardiac output and volume status based on pulmonary artery catheter monitoring in critical care settings lead to improved patient outcomes compared to noninvasive and less invasive techniques?

**Question 4:** What complications and adverse events associated with pulmonary artery catheter monitoring have been reported?

# Chapter 2. Methods

This report on the benefits and harms of pulmonary artery catheter (PAC) use in critical care settings is based both on a systematic review of the literature and on narrative reviews. For the background information on PACs, we used a narrative review approach to describe the devices and techniques that are currently used to assess cardiac output and volume status in critical care settings, and the indications for PAC placement (Questions 1 & 2). For questions regarding the effect of and adverse events associated with PAC, we performed systematic reviews.

The approach, methodology, and criteria used were agreed upon by consensus of the Evidence-based Practice Center (EPC) clinician-methodologists, an expert in cardiology and intensive care based at Tufts Medical Center, Centers for Medicare & Medicaid Services (CMS) staff organizing a Medicaid Coverage Advisory Committee (MCAC) meeting on PAC, and staff at the Agency for Healthcare Research and Quality (AHRQ) with methodological expertise.

## Search Strategy

A comprehensive search of the scientific literature was conducted to identify relevant studies addressing the key questions. In September 2006 we searched MEDLINE® (from 1966 to present), MEDLINE® In-Process & Other Non-Indexed Citations, and Cochrane databases (3rd quarter 2006) English language studies of adult humans to identify articles relevant to each key question. We also reviewed reference lists of related systematic reviews and selected narrative reviews and primary articles. In electronic searches, we used various terms for pulmonary artery catheters (including Swan-Ganz), limited to adult humans, and relevant research designs (see **Appendix A** for complete search strategy). We did not systematically search for unpublished data.

## Study Selection

We assessed titles and/or abstracts of citations identified from literature searches for inclusion, using the criteria described below. Full-text articles of potentially relevant abstracts were retrieved and a second review for inclusion was conducted by reapplying the inclusion criteria. A low threshold was used to retrieve articles for full rescreening. Results published only in abstract form are not included in our reviews because adequate information is not available to assess the validity of the data and these reports have generally not been peer-reviewed.

### Population and condition of interest

We included studies of adults (≥ 18 years old) with conditions requiring inpatient hemodynamic monitoring. Conditions included but were not limited to heart failure, preoperative evaluation with compromised left ventricular function (for cardiac or noncardiac surgery), dialysis (to assess volume status), acute respiratory distress syndrome, and related pulmonary conditions. We excluded studies of preheart transplant patients for whom evaluation with PAC is a standard method for assessing transplant status, and the pregnancy-related population including postpartum women, a population considered to have limited applicability to the Medicare population in the intensive care setting.

## Interventions of interest

The intervention of interest was PAC used for "treatment management", as either intermittent or continual measurement devices. This description of the intervention of interest is purposely broad to avoid excluding potentially relevant studies. It includes studies where PAC was used to assist with the management of patients after initial diagnoses are made. Studies of PACs that were used only for the purpose of initial diagnosis (e.g., type of shock or cause of hypotension) or that were used for single-reading measurements (e.g. "in and out") were excluded.

## Comparators of interest

The acceptable comparators of interest included other noninvasive and less invasive techniques for the management of cardiac output and volume status. We also included studies that used "no PAC" as a comparator. We excluded studies that used experimental devices (where PAC is the reference standard).

## Outcomes of interest

We analyzed clinical outcomes of greatest interest to CMS, in discussion with our domain expert. We restricted our evaluation to those outcomes deemed clinically important and did not include surrogate outcomes.

Outcomes of interest included:

- Mortality due to all causes
- Length of hospital and intensive care unit stay
- Medical morbidities (e.g., cardiac or pulmonary events)
- Duration of ventilation
- Quality of life, using any quality of life measure or any measure of symptom relief
- Optimization of treatment (e.g., ACE inhibitor maximization)
- Adverse events and complications associated with PAC use (Question 4), including, but not limited to
    - Pneumothorax
    - Bleeding
    - Arrhythmia
    - Infection
    - Insertion complications
    - Death
    - Urgent surgery

## Study designs of interest

For clinical outcomes, we included only randomized controlled trials, excluding nonrandomized prospective studies, noncomparative studies, and retrospective studies (including case-control studies). There was no minimum sample size requirement.

For adverse events, we also included studies of any design with at least than 500 patients with PACs. Review articles were also included for lists of adverse events and some estimates of rates of adverse events from primary studies that these reviews evaluated.

## Data Extraction

Items extracted included study year, country, setting, funding source, study design, eligibility criteria, and type of PAC use (see **Appendix B** for a sample data extraction form). For randomized controlled trials (RCTs), we recorded the method of randomization, allocation concealment, blinding, and whether results were reported on an intention-to-treat basis. Specific population characteristics included demographics such as age and sex, and baseline severity of disease. Details regarding PAC management, including who inserted PAC and the duration of PAC exposure were also extracted.

For each outcome of interest, baseline, followup, and change from baseline data were extracted, including information of statistical significance. For most outcomes, only data from the last reported time point was included. When outcome data were reported as overall outcomes, without a specific time point, the mean or median time of followup was used. All adverse event data were extracted.

## Quality Assessment

We assessed the methodological quality of studies based on predefined criteria. We used a 3-category grading system (A, B, C) to denote the methodological quality of each study. This grading system has been used in most of the previous evidence reports from the Tufts EPC as well as in evidence-based clinical practice guidelines (21;22). This system defines a generic grading system that is applicable to varying study designs including randomized and nonrandomized comparative trials, cohort, and case-control studies. For randomized trials, we mainly considered the methods used for randomization, allocation concealment, and blinding as well as the use of intention-to-treat analysis, the report of dropout rate and the extent to which valid primary outcomes were described, as well as clearly reported. Studies were not rejected due to poor quality.

**A (good)**

Category A studies have the least bias and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality including the following: a formal randomized controlled study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; less than 20 percent dropout; clear reporting of dropouts; and no obvious bias.

For studies of adverse events, it must be a prospective design.

**B (fair/moderate)**

Category B studies are susceptible to some bias, but not sufficient to invalidate the results. They do not meet all the criteria in category A because they have some deficiencies, but none likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

For studies of adverse events, it must be a prospective design.

**C (poor)**

Category C studies have significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information, or discrepancies in reporting.

All retrospective studies of adverse events were graded C.

# Applicability Assessment

Applicability addresses the relevance of a given study to a population of interest. Every study applies certain eligibility criteria when selecting study subjects. Most of these criteria are explicitly stated (e.g., disease status, age, comorbidities). Some may be implicit or due to unintentional biases, such as those related to location (e.g., multicenter vs. single center, intensive care vs. all inpatients), years of PAC use, and other issues. The applicability of a study is dictated by the key questions, the populations, and the interventions that are of interest to this review, as opposed to those of interest to the original investigators.

To address this issue, we categorized studies within a target population into 1 of 3 levels of applicability that are defined as follows:

| | |
|---|---|
| High | Sample is representative of Medicare population in relevant settings. Patients' age (older adult), gender, spectrum of disease severity and type, etc. are representative of population of interest. PACs were used within past 10 years (1997-2006). |
| Moderate | Sample is an important subgroup of population of interest. Possibly limited to a narrow or young age range, type of disease, gender etc. PACs were used within past 20 years (1987-2006). |
| Low | Sample represents only a narrow, atypical subgroup of population of interest. |

# Data Synthesis

## Metaanalyses

Metaanalysis was performed to examine whether therapeutic management based on PAC monitoring led to improved patient outcomes compared to noninvasive and less invasive techniques, when sufficient data were available. We used the DerSimonian and Laird's random effects model for all syntheses (23). The random effects model assigns a weight to each study based both on the individual study variance and the between-study heterogeneity. Compared with the fixed effect model, the random effects model is more conservative in that it generally results in broader confidence intervals when between-study heterogeneity is present. We tested for heterogeneity using Cochran's Q and assessed its extent with $I^2$, which evaluates the proportion of between study variability that is attributed to heterogeneity rather than chance (24;25).

**Mortality outcome**

For mortality, we used the random effects model for binary data to combine studies. Studies that reported mortality rates for both PAC and control groups were included in the metaanalysis. The odds ratio (OR) and its standard error (SE) were calculated for each study from the raw

events data. Studies that reported only data on (adjusted or unadjusted) OR and SE were also included in the analysis with an assumption of symmetrical confidence intervals. When only exact *P* values were reported (instead of SE), we back-calculated the SE from the *P* value.

**Length of stay**

For the outcomes length of hospital stay and length of intensive care unit stay we used the random effects model for effect size (the mean between-group difference in the length of stay) to combine studies. Studies were included only if they reported sufficient data to estimate both the effect size and the SE of the effect size. When only exact p values were reported, we back-calculated the SE from the *P* value.

**Subgroup Analyses**

To explore potential reasons for differences of results across studies, we performed subgroup analyses by types of comparison (PAC vs. no PAC; PAC vs. CVP) for all metaanalyses.

## External Review

Five cardiologists and/or pulmonary and critical care medicine specialists kindly reviewed early drafts of this report. Each comment was addressed and responded to, and revisions were made. The authors of the report maintain full responsibility for the content and judgments made herewithin. The final report has not been endorsed report by the reviewers. Staff at CMS and AHRQ also provided comments, but the findings and conclusions do not necessarily represent the views of AHRQ or CMS. Therefore, no statement in this report should be construed as an official position of the Agency for Healthcare Research and Quality, the U.S. Department of Health and Human Services, or the Centers for Medicare and Medicaid Services.

# Chapter 3. Results

## **Question 1:** What types of devices and techniques are currently used to assess cardiac output and manage volume status in critical care settings (including operating and recovery rooms)?

Question 1 has been answered based on a narrative review of the literature.

Measurement of the cardiac output is an essential part of any hemodynamic study. An ideal technique for cardiac output measurement should be accurate, reproducible, easy to perform, cost-effective, able to perform in varied settings and should not be associated with any excess morbidity or mortality to the patients. The general technique and uses of PAC has been described in the introduction; this section will briefly describe various devices that utilize invasive or noninvasive techniques and are used to monitor hemodynamic status in critical care settings. The invasive techniques include:

- PAC using various methods based on (a) the Fick Principle, (b) the indicator dye dilution technique and (c) thermodilution method
- Central venous pressure (CVP) catheter
- Transesophageal Doppler measurement
- Pulse contour analysis methods

The noninvasive techniques include:

- Echocardiography and Doppler echocardiography
- Impedance cardiography
- Partial $CO_2$ consumption/Inert gas exchange
- Others such as nuclear imaging and left ventriculography

### Invasive technologies

**Various methods that utilize PAC**

The method using Fick principle estimates the cardiac output as the ratio between oxygen consumption and arteriovenous difference in oxygen. The Fick principle involves measuring $VO_2$ consumption per minute using a spirometer and a $CO_2$ absorber, the oxygen content of mixed venous blood (pulmonary artery), and oxygen content of peripheral arterial blood. Adolf Fick in 1870 postulated that the oxygen uptake in the lungs is entirely transferred to the blood. However this estimation is accurate only when the hemodynamic status is sufficiently stable to allow constant gas diffusion during the mean transit time through the lungs. The Fick principle has also been applied to any gas diffusing through the lungs and this also has been adapted as a noninvasive technique.

The indicator dye method first proposed by Stewart in 1890, and subsequently modified by Hamilton, which utilizes addition of a known concentration of dye indicator to mix with blood. The final dye concentration is determined using a densitometer. With continuous sampling, a time-concentration or indicator dilution curve can be plotted and cardiac output is estimated using the Stewart Hamilton equation.

Thermodilution method applies the dye dilution principle using temperature as the indicator. A known quantity of solution at a known temperature is injected rapidly into the right atrium and the temperature of the blood admixed with the solution is measured using a

thermistor in the PAC in the pulmonary artery. The time-temperature curve is plotted and the cardiac output is calculated using a modified Stewart Hamilton equation. Continuous thermodilution uses a 10 cm long thermal filament to emit energy pulses, and the pulmonary artery temperature changes are identified using a computerized algorithm using the thermodilution washout curve and applying the modified Stewart Hamilton equation. The cardiac output is averaged over 30 to 60 seconds and displayed as a continuous reading.

**Central venous pressure (CVP) catheter**

CVP was first described in 1969 (26) and is frequently used for measuring right atrial pressure and estimation of the intravascular volume status. CVP is inserted through a major vein in the neck or chest, placed in superior vena cava or right atrium and water manometer or electronic transducer attached to the catheter monitors the pressure. The common indications for CVP include: major operative procedures, intravascular volume assessment in acute kidney failure, inadequate peripheral access, frequent venous sampling, venous access for vasoactive or chronic drug administration, rapid infusion of intravenous fluids, and other uses such as insertion of transvenous pacing wires and for plasmapheresis or hemodialysis. The right atrial pressures can be estimated using CVP measurements and circulatory status can be manipulated. However in critically ill patients with compromised cardiovascular status, such estimations of right heart pressures do not correlate well with PAOP; thus making CVP a less favored device to monitor circulation status.

**Transesophageal Doppler measurement**

Transesophageal Doppler estimates continuous noninvasive and real time monitoring of cardiac output from measurements of aortic flow velocities. The device consists of a continuous wave Doppler transducer mounted at the tip of a transesophageal probe that is placed in the midesophagus directed at the descending aorta. The probe is connected to a monitor that displays the aortic flow velocity profiles from the spectral analysis of the Doppler signal. Bedside measurement of the crosssectional area of the descending aorta can be performed either by using transesophageal echocardiography or estimated based on the patient's age, weight, and height by a nomogram incorporated to the transesophageal Doppler device. The stroke volume is then calculated from the maximum aortic velocity-time integral and the aortic crosssectional area to obtain blood flow volume per heartbeat. Cardiac output is estimated from the heart rate and stroke volume, which in turn is based on assumptions of accurate measurements of aortic flow velocity profile, estimated crosssectional area of the aorta, and variations in the descending aortic blood flow. However this device does not provide complete estimates of cardiac pressures. The device use is limited to patients who are unconscious, well sedated, or anesthetized and has the potential side effect of trauma to the esophagus.

**Pulse contour methods**

The pulse contour analysis estimates cardiac output measurement indirectly that is computed from pressure pulsation based on the classic Windkessel model described by Otto Frank in 1899. The majority of the pulse contour methods are explicitly or implicitly based on this model and estimate beat-to-beat stroke volume. They relate an arterial pressure or pressure difference to a flow or volume change that are derived from a major peripheral artery. Currently available pulse contour methods include PiCCO (Pulsion), PulseCO (LiDCO) and Modelflow (TNO/BMI). All three pulse contour methods use an invasively measured arterial blood pressure that needs to be calibrated. The calibration generally involves injecting cold saline solution into a

central vein and temperature changes are measured using a thermistor on the arterial end (other techniques are also used). Output of these pulse contour systems is calculated on a beat-to-beat basis, and the data is averaged over 30 seconds (27). While this technique provides continuous measurement of cardiac output, records arterial and central venous pressures, and calculates many hemodynamic variables its usefulness is limited to patients in sinus rhythm.

## Noninvasive technologies

Noninvasive cardiac imaging can be utilized to give a reasonable estimate of cardiac output and function even though specific pressures within cardiac chambers cannot be recorded.

### Echocardiography and Doppler echocardiography

Echocardiography utilizes ultrasound techniques to produce a two or three-dimensional view of the heart. The ultrasound images cardiac structures including the valve structure and function, valvular regurgitation, the morphology of the chambers, and any abnormal communication between the right and left side of the heart. It also measures cardiac output and left ventricular ejection fraction. Echocardiography is usually used with Doppler ultrasound to estimate the flow related measurements. Limitations include poor acoustic window and poor transmission of ultrasound in artificially ventilated patients.

Transthoracic Doppler measurement monitors cardiac output similar to trans-esophageal Doppler, but utilizes a noninvasive technique. The device consists of a continuous wave Doppler transducer mounted at the tip of a transthoracic probe that is placed in the sternal notch directed at the ascending aorta. Its noninvasive technique makes it useful to monitor cardiac output in conscious patients. Limitations of this device include lack of reliable estimates of cardiac output due to difficulty in maintaining a constant angle between the ascending aorta and the probe. The device gives only indirect estimates of vascular or cardiac pressures.

### Impedance cardiography

Hemodynamic measurements of cardiac output using thoracic electrical bioimpedance (TEB) devices are a form of plethysmography that relates changes in thoracic electrical conductivity to changes in thoracic aortic blood volume and blood flow. TEB measures cardiac output, cardiac index, stroke volume, and ejection fraction. TEB utilizes the principle that resistance to electrical current in the thorax varies in relation to the amount of blood in the aorta. It works by introducing a low voltage alternating current between sets of electrodes or leads that are placed on the skin surface over the thorax. The difference between the voltage that is introduced by the device and that which the device senses from the thorax indicates the amount of resistance or impedance that the electrical current encounters. The impedance, in conjunction with electrocardiographic results and an estimation equation for stroke volume estimates cardiac output from which other cardiac measures may also be computed (28). Cardiac index is one other cardiac parameter that can be calculated from bioimpedance measurements. Currently, some of the electrical bioimpedance devices in the marketplace are Bio Z® (Cardiodynamics, Inc.), TEBCO (Thoracic Electrical Bioimpedance Cardiac Output, Hemo Sapiens, Inc.).

### Partial $CO_2$ consumption/Inert gas exchange

Inert gas rebreathing, also known as foreign gas rebreathing, utilizes the uptake of an indicator gas from the lungs for measuring cardiac output. Foreign gases used in the rebreathing method are physiologically inert, blood soluble gases such as acetylene, carbon dioxide, and nitrous oxide. This technique entails the use of a closed rebreathing system where a very small

amount of an inert gas is inhaled from a rebreathing bag. Patients breathe through a mouthpiece with the nasal passages closed by a nasal clip. The uptake these gases are measured continuously and simultaneously at the mouthpiece by a photoacoustic gas analyzer in the device. The solubility of these gases in the blood and the rates at which they are absorbed in the lungs give an estimate of the pulmonary blood flow. Measurement of the concentration curve of the inert gas and calculation of the washout rate with a respiratory mass spectrometer or infrared photoacoustic gas analyzer estimates the cardiac output. Higher cardiac output results in a higher disappearance rate measured as the slope of the gas curve.

Currently available devices include the NICO (Novametrix) system, a noninvasive device that applies Fick's principle on $CO_2$, and the Innocor TM (Innovision) that uses oxygen-enriched mixture containing two foreign inert gases typically 0.5% nitrous oxide ($N_2O$) and 0.1% sulphur hexafluoride ($SF_6$). Initial clinical trials have evaluated the agreement between inert gas rebreathing and other techniques such as thermodilution. However, these clinical trials were small, mainly focused on specific patient groups. The limitations of these devices include changing patterns of ventilation that may have an unpredictable influence on measurements and lack of measurement of vascular pressures.

## **Question 2:** What are the specific indications for pulmonary artery catheter placement in critical care settings?

Question 2 has been answered based on a narrative review of the literature. The general technique and uses of PAC has been described in the introduction chapter and under question 1. PAC can be an aid to diagnosis as well as guide therapy. The specific indications for PAC in critical care settings are tabulated here.

**Table 1. Specific indications for PAC in critical care settings**

| |
|---|
| **Diagnosis and Evaluation** |
| Differential diagnosis of shock |
| Cardiogenic shock |
| Septic shock |
| Hypovolemic shock |
| Evaluation of pulmonary edema |
| Cardiogenic pulmonary edema |
| Non-cardiogenic pulmonary edema |
| Etiology of cardiac failure |
| Restrictive pericarditis |
| Constrictive pericarditis |
| Cardiac tamponade |
| Evaluation of cardiac structures |
| Valvular diseases |
| Intracardiac shunts |
| Evaluation of shock in setting of acute myocardial infarction (AMI) |
| Evaluation of primary pulmonary hypertension |
| Evaluation in renal failure to assess volume status |
| **Therapeutic Management** |
| Guide therapy in advanced heart failure |
| Guide therapy in complicated AMI |
| Treatment of primary pulmonary hypertension |
| Adjust hemodynamics during major surgery |
| Management of patients with multiorgan failure |
| Ventilator management |
| Guide pharmacologic therapy (vasopressors, inotropes, and vasodilators) |
| Guide fluid management (major bleed, burns, sepsis, and acute kidney failure) |

## Question 3: Does therapeutic management of cardiac output and volume status based on pulmonary artery catheter monitoring in critical care settings lead to improved patient outcomes compared to noninvasive and less invasive techniques?

A total of 16 trials (5;7;8;14;15;29-40) met eligibility criteria of studies that examined whether therapeutic management based on PAC monitoring led to improved patient outcomes compared to noninvasive and less-invasive techniques. Fifteen trials reported data on mortality, 13 of which also reported data on the length of hospital stay and/or on the length of ICU stay. Eleven trials reported comparative rates of various medical morbidities.

The trials were clinically heterogeneous. The articles were published between 1985 and 2006. They differed widely in their design, eligibility criteria and settings, resulting in very different groups of patients being analyzed (**Table 2**). Nine studies compared PAC to no PAC, seven compared PAC to CVP. Five trials were conducted in medical or general intensive care units, nine in surgical intensive care units, one in both medical and surgical intensive care units, and one in a cardiac care unit. Only four studies included a broad range of patients, not restricted to a specific set of surgeries or medical conditions (2 medical or general units (32;35), the medical and surgical units study (31), and one surgical unit study (39;41)). Only Harvey 2005 and Rhodes 2002 explicitly included patients who were deemed to require PAC ("should be managed with a PAC"; "requiring a PAC") by their treating physicians (32;35). However, Rhodes 2002 excluded patients "for which the standard of practice... is to supra-normalize their circulation perioperatively with the use of PAC" and one patient was excluded because their physician believed it was unethical to withhold PAC. And Harvey 2005 excluded patients for whom there was "lack of equipoise from [their] treating physician." As described in their eligibility criteria, studies tended to focus on populations that were clinically ill, but not on populations for whom intensive, invasive hemodynamic monitoring was thought to be of particular value; 11 of the 16 studies excluded patients for whom PAC was deemed necessary or who were at high risk (5;7;14;15;29-31;33;35;36;40). Across the studies that reported data, between 0.5 and 52 percent of potentially eligible patients were excluded because presence of severe medical conditions or physician determination that withholding PAC would be inappropriate or unethical (though most studies did not report numbers of excluded patients); among the seven studies that reported data, a median of 23 percent of patients were excluded for these reasons. Most studies excluded patients for whom PAC may be of most value (e.g., post-myocardial infarction, valvular disease, poorly compensated congestive heart failure). Pearson 1989 reassigned patients for whom the anesthesiologist judged that PAC was indicated to separate cohorts who received PAC (34).

None of the studies established a specific protocol for how data from PAC (or CVP) were acted on; although the Shoemaker study stated that the therapeutic goals in the protocol group required sufficient quantities of fluids and inotropic agents to attain the therapeutic goals (39;41) and Wheeler 2006 had goals for maintaining blood pressure, urine output, and effective circulation based in part on PAC or CVP readings (15). Most studies did not report any information on how PAC data were handled or how treatment management was affected by the PAC data. In fact, among the studies that described treatments or protocols, most explicitly stated that no protocol was established and/or that clinical management was at the discretion of the treating clinicians. Four studies reported on the effect of PAC on use of treatments. Two

studies found greater use of inotropic agents (Sandham 2003 (37), Wheeler 2006 (15)); but only Sandham 2003 reported greater use vasodilators, antihypertensive medications, packed red blood cells, and colloid. Pearson 1989 (34) reported no significant difference in duration of vasopressor administration and Wheeler 2006 reported no difference in use of fluids and diuretics (15). Harvey 2005 found that the most frequently reported changes in management due to PAC were fluid infusion, introduction and change in dose of vasoactive drugs (32).

Most studies included a majority of patients who were age 65 years or older, as judged by study mean or median ages. The overall (unadjusted) average age across studies was approximately 62 years. No study specifically included or excluded patients based on older age (65 years or older). Three studies included relatively young patients (compared to most studies), with mean ages less than 60 years (Wheeler 2006 (15), ESCAPE 2005 (14), Shoemaker 1988 (39)), while two had relatively older patients with mean ages over 70 years (Sandham 2003 (37), Schultz 1985 (38)). The different ages are likely due to the clinical heterogeneity related to various eligibility criteria and settings. No study evaluated whether outcomes differed based on patient ages. Across outcomes, there were no clear differences in outcomes based on the average age of patients.

Among the 9 studies that reported information about crossover (e.g., assignment to the control or CVP group, but received PAC regardless), the rate of crossovers was less than 2 percent in 4 studies (5;15;35;37) and up to 10 percent in 3 studies (14;32;36). In the Guyatt 1991 trial, 8 of 17 patients (47 percent) randomized to the control group had PAC at some point during their hospital stay because of "their deteriorating status;" 7 of these patients died. In the Pearson 1989 trial, 47 of 74 patients (64 percent) initially randomized to CVP were rerandomized to additional groups who received PAC (34). The high crossover rates in these studies calls into question the validity of the comparison. However, as these problematic studies are small there inclusion or exclusion from the metaanalyses do not substantially alter the summary results. With the goal of best approximating intention-to-treat analyses, where patients are analyzed in the arm to which they were assigned, regardless of ultimate treatment, we have included all studies in metaanalyses regardless of crossover rates. It should be noted though that high crossover rates tend to push results toward the null (finding no statistically significant difference between interventions).

Metaanalyses were performed for several clinical outcomes, where data permitted. Studies in all metaanalyses were grouped by type of comparisons (PAC vs. "no PAC"; PAC vs. CVP). Subgroup analyses on the two types of comparisons were performed. An overall effect estimate combining all studies in both groups was also calculated for each metaanalysis. Studies in each group of comparison were sorted by the study setting in the following order: cardiac or critical care unit (CCU), medical intensive care unit (MICU), intensive care unit (ICU), medical or surgical intensive care unit (M/SICU), and surgical intensive care unit (SICU). Although the study setting may be a source of heterogeneity, the number of available studies in all metaanalyses was too small to perform subgroup analyses based on study settings.

**Table 2. Settings and populations of randomized trials of pulmonary artery catheterization**

| Study, Year | Setting | Major eligibility criteria (Percent of recruited patients excluded*) | Hemodynamic status<br>Other invasive/noninvasive tests for CVD function | Patients' diagnoses | Severity of disease<br>PAC | <br>Control |
|---|---|---|---|---|---|---|
| **PAC vs No PAC** | | | | | | |
| Guyatt, 1991 (31) | M/SICU | Intensive care, medically sick, and postoperative and trauma who might benefit from PAC<br>**Exclude:** Patients in whom the clinician felt that PAC was an ethical imperative (35%) or contraindicated (20%) [Other 22%] | On assisted ventilation with PEEP≥10 cm $H_2O$, MBP<65 mm Hg or $PO_2$ <60mmHg with CVP ≥10 cm $H_2O$, urine output <0.5mL/Kg bw/hr in the presence of hypoxemia<br>CVP | Sepsis, MI, respiratory failure, trauma, perioperative, gastrointestinal bleeding or others | APACHE<br>20 | <br>23 |
| Valentine, 1998 (7) | SICU | Elective abdominal aortic reconstruction<br>**Exclude:** Kidney failure (2%) or additional vascular procedures needed (21%) | nd<br>Adenosine thallium scintigraphy | AAA with normal cardiac status or fixed defects | nd | |
| Bonazzi, 2002 (30) | SICU | Elective infrarenal abdominal aortic reconstruction, without clinical and echocardiographic evidence of CAD<br>**Exclude:** High risk patients (nd) | Ejection fraction ≥50<br>Transthoracic echocardiography | Infrarenal AAA | APACHE II<br>7 | <br>7 |
| Berlauk, 1991 (29) | SICU | In situ vein graft bypass for limb salvage<br>**Exclude:** Clinical settings for which literature supports the use of PAC, ie, unstable patients (nd) | PAC: 60% SVR>1000 dynes/sec $cm^{-5}$, 13% CI<2.8 L/min/$M^2$, 22% PAWP>15 mm Hg<br>Control: Not done<br>CVP | Lower-extremity atherosclerotic arterial occlusive disease | nd | |
| Harvey, 2005 (32) | MICU | ICU admission, identified "as someone who should be managed with a PAC"<br>**Exclude:** "Lack of equipoise from treating physician" (9%) [Other 11%] | nd | Acute respiratory failure, multiorgan dysfunction, decompensated heart failure | APACHE II<br>22<br>SOFA<br>9 | <br>23<br><br>9 |

[continued]

**Table 2. Continued**

| Study, Year | Setting | Eligibility criteria | Hemodynamic status / Other invasive/noninvasive tests for CVD function | Patients' diagnoses | Severity of disease (PAC / Control) |
|---|---|---|---|---|---|
| **PAC vs No PAC, continued** | | | | | |
| Sandham, 2003 (37) | SICU | Major abdominal, thoracic, vascular, or orthopedic surgery; ASA class III or IV risk for surgery<br>**Exclude:** None (†) | nd<br>CVP | CAD | ASA class III or IV risk<br>Goldman index 8 |
| Richard, 2003 (36) | ICU (mixed units) | ICU admission with shock and/or ARDS<br>**Exclude:** Shock for >12 hr or ARDS for <24 hr, hemorrhagic or some with cardiogenic shock, moribund (nd) | Respiratory rate ≥20/min, $PaCO_2$ ≤32 mmHg, or acute decrease in $PaO_2/FIO_2$ to ≤200 mmHg<br>CVP, echocardiography | Shock and/or ARDS | SOFA 10 / 10<br>SAPS II 54 / 54<br>Odin 3.4 / 3.4<br>Brussels 2.7 / 2.7 |
| ESCAPE, 2005 (14) | CCU | Severe symptomatic heart failure<br>**Exclude:** Kidney failure, use of inotropic drugs, crossover to PAC for urgent management unlikely based on recent medical history (nd) | PAC: LVEF=19%, SBP=106 mm Hg<br>Control: LVEF=20%, SBP=106 mm Hg | Advanced heart failure | MLHF 74 / 73 |
| Rhodes, 2002 (35) | ICU | ICU admission, identified as requiring a PAC<br>**Exclude:** Elective high-risk surgery requiring supranormalized circulation (nd); unethical to withhold PAC (0.5%) | PAC: $PaO_2/FIO_2$ (kPa)=25, MAP=79 mm Hg<br>Control: $PaO_2/FIO_2$ (kPa)=23, MAP=78 mm Hg<br>CVP | Shock, multi-organ dysfunction, kidney failure, ARDS | APACHE II 22 / 19<br>SOFA 7 / 7 |
| **PAC vs CVP** | | | | | |
| Isaacson, 1990 (33) | SICU | Abdominal aortic reconstructive<br>**Exclude:** Inoperable, severe CAD or other condition where PAC monitoring would be mandatory (24%) [Other 23%] | LVEF ≥40%<br>CVP | Abdominal aortic diseases | ASA class III or IV risk |

[continued]

**Table 2. Continued**

| Study, Year | Setting | Eligibility criteria | Hemodynamic status<br>Other invasive/noninvasive tests for CVD function | Patients' diagnoses | Severity of disease<br>PAC | <br>Control |
|---|---|---|---|---|---|---|
| **PAC vs CVP, continued** | | | | | | |
| Shoemaker, 1988; 1990 (39;41) | SICU | High risk of dying after surgery<br>**Exclude:** Not ill enough to require intensive monitoring (12%) | nd<br>CVP | One or more of the high risk diseases including severe cardiorespiratory illness, extensive ablative surgery, multiple trauma, etc. | nd | |
| Wheeler, 2006 NHLBI (15) | ICU | Acute lung injury receiving ventilation, $PaO_2/FIO_2$<300, pulmonary edema but not due to left atrial hypertension<br>**Exclude:‡** Physician refusal (15%), presence of PAC (19%), severe medical conditions (52%)<br>[Other 24%] | PAC: MAP=78 mm Hg, vasopressor use=36%, met shock criteria=37%<br>Control: MAP=77 mmHg, vasopressor use=30%, met shock criteria=32%<br>CVP | Acute lung injury | APACHE III<br>95 | <br>94 |
| Bender, 1997 (5) | SICU | Infrarenal aortic reconstruction and/or lower limb revascularization<br>**Exclude:** Recent severe cardiac disease (10%), proximal vascular cross-clamp (5%) | PAC: 8≤PAOP≤14 mm Hg, CI≥2.8 L/min/$m^2$, SVR≤1100 dyne-sec/$cm^2$<br>Control: nd<br>Radial artery catheter | Aortic and non aortic vascular diseases with rest pain, ulcer, claudication, gangrene, aneurysm | nd | |
| Schultz, 1985 (38) | ICU | Hip fracture, underprivileged, nutritionally depleted, poor physiologic condition<br>**Exclude:** nd | PAC: RAP=3.6 mm Hg, PAWP=6.8 mm Hg<br>CVP | Hip fracture | nd | |
| Pearson, 1998 (34) | SICU | Elective cardiac surgical patients<br>**Exclude:** nd<br>**N.B.** Reassigned to PAC arm if PAC was indicated | PAC: LVEF=52%<br>CVP: LVEF=64%<br>CVP, Fiberoptic infrared mixed venous oxygen ($SvO_2$) measuring PAC | Elective cardiac surgery | nd | |
| Joyce, 1990 (40) | SICU | Elective infrarenal aortic reconstructive surgery; "low risk" only<br>**Exclude:** unstable or poor cardiac function (nd) | PAC: LVEF>0.50, PAWP=9 mmHg, CI=2.6 L/min/$m^2$, CVP=6, MAP=105<br>Control: CVP=8, MAP=86<br>Gated radionucleotide scan, CVP | AAA | nd | |

AAA, Abdominal aortic aneurysm; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ASA, American Society of Anesthesiologists; BP, blood pressure; bw, body weight; BSA, body surface area; CAD, coronary artery disease; CCU, cardiac care unit; CI, cardiac index; CRF, chronic renal failure; CVP, central venous pressure; $DO_2$, oxygen delivery; FEV1, Forced expiratory volume in one second; FIO2, Fraction of inspired oxygen; ICU, intensive care unit; LV, left ventricular; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MBP, mean blood pressure; MI, myocardial infarction; MICU, medical intensive care unit; M/SICU, medical/surgical intensive care unit; MLHF, Minnesota Living with Heart Failure questionnaire; nd, no data; PAC, pulmonary artery catheter; PaCO2, arterial partial pressure carbon dioxide; PaO2, arterial partial pressure oxygen; PAOP, pulmonary artery occlusion pressure; PAWP, pulmonary artery wedge pressure; PEEP, positive end expiratory pressure; RAP, Right atrial pressure; SAPS II, Simplified Acute Physiology score II; SBP, systolic blood pressure; SICU, surgical intensive care unit; SOFA, sepsis-related organ failure score; SVR, systemic vascular resistance.

* Percent of total number of potentially eligible patients who were excluded for the given reasons.
† All participating physicians agreed to refer all their eligible patients. Nevertheless, 28% of patients declined to participate, 10% had no bed available in the ICU, and 10% were not enrolled because their physicians failed to refer them to the study.
‡ Percentages extrapolated from appendix Table 1. Assumed that randomized patients were not included in percentages. Double counting of patients occurred because “one of several [exclusion] reasons” data used.

## Mortality (Figure 1, Table 3)

A total of 15 trials reported data on death in patients received PAC monitoring and in the control patients in critical care settings (5;7;8;14;15;29-39). Of these, nine compared the mortality outcome of patients received PAC monitoring with those who received no PAC monitoring (7;14;29-32;35-37) and six compared PAC to patients received CVP monitoring (5;15;33;34;38;39). One study was in a CCU setting, one was in a MICU setting, four were in ICU settings, one was in a M/SICU setting, and eight were in SICU settings. Six studies each were of good or moderate methodological quality (Grade A or B, respectively) and three studies were of poor quality (Grade C). Two had wide applicability, 6 moderate applicability, 7 narrow applicability.

The overall odds ratio of death was 1.03 (95% CI 0.9, 1.2) comparing patients who received PAC monitoring to control patients who did not receive PAC monitoring in critical care settings. There was no statistically significant heterogeneity across the 15 studies. In the nine studies comparing PAC to no PAC monitoring, the random effects combined odds ratio of death was 1.03 (95% CI 0.9, 1.2). In the five studies comparing PAC to CVP monitoring, the random effects combined odds ratio of death was 0.96 (95% CI 0.5, 2.0). There was no statistically significant heterogeneity within each subgroup, and there was no statistically significant difference between the combined ORs in the two subgroups (**Figure 1**). Rhodes 2002, in contrast to the other trials, reported only an adjusted OR of death. Excluding this study from the analysis did not alter the summary estimates.

Schultz 1985 reported the greatest, and only statistically significant, benefit with PAC (38). This study was the first randomized trial that compared the outcomes of PAC monitoring to that of CVP monitoring in 70 generally older (mean age 72, range 40-95 years), underprivileged and nutritionally depleted hip fracture patients with poor physiologic condition. The trial showed a "highly significant" reduction in the mortality rate associated with the PAC monitoring (2.9% vs. 29%, $P < 0.01$). It was rated poor methodological quality (Grade C). The study provided no clear explanation for why such a large difference in mortality rates was found and no definitive explanation was found why this study differed from later trials. It is possible that, as has been found in other fields, this result occurred by chance and because of the large effect, in the absence of previous trials, was more likely to be published than if no benefit were found (42).

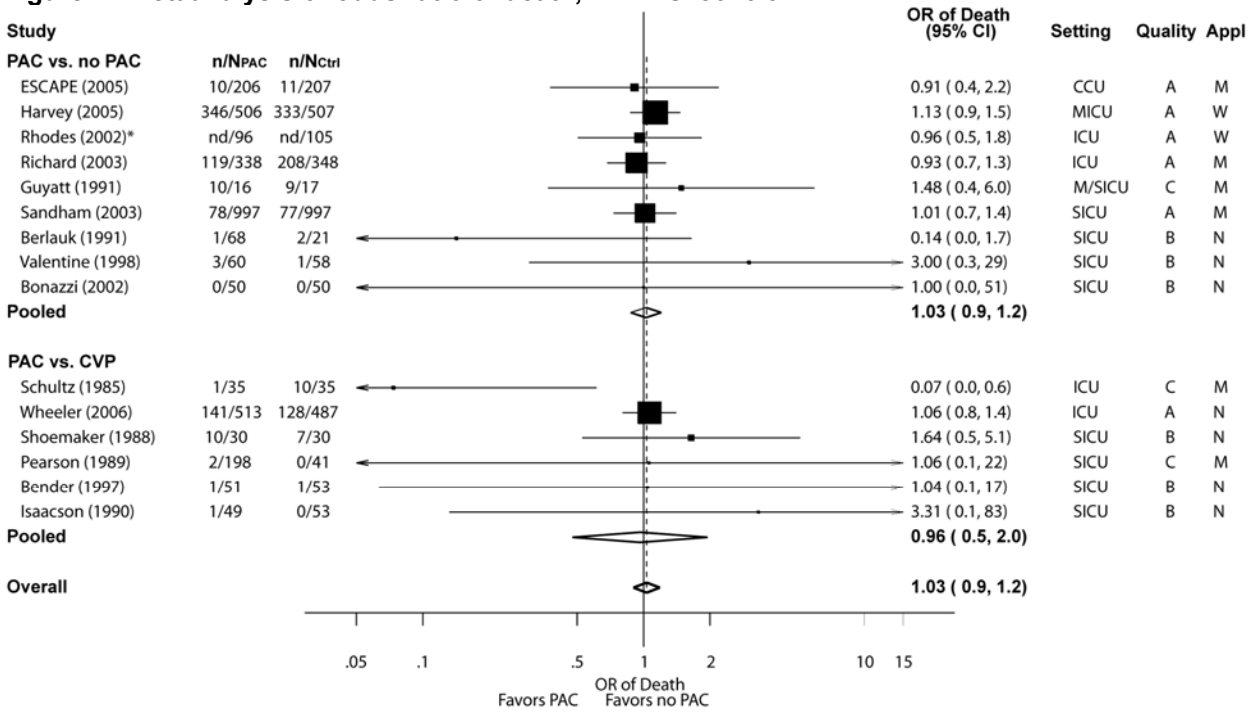
Two studies reported subgroup analyses of mortality. Sandham 2003 in a trial of almost 2000 patients undergoing high risk surgical procedures compared multiple subgroups (37). They found no evidence of variation of effect according to center (hospital), American Society of Anesthesiologists (ASA) risk class, type of surgery, sex, age, or New York Heart Association (NYHA) cardiac function class. Richard 2003 in a trial of almost 700 patients with shock or acute respiratory distress syndrome also found no difference in effect across subgroups based on diagnosis or the Simplified Acute Physiology Score II (36). However, neither study was powered to detect differences in mortality among subgroups, so the failure to find statistically significant differences does not rule out the possibility of real differences among subgroups.

**Table 3. Mortality in patients with PAC vs control in randomized controlled trials**

| Study, Year | Setting | No. Analyzed | | Mean Age (yr)[a] | % Male[a] | Outcome | Metric/ Units | Results | | | Quality | Applicability |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | PAC | Control | | | | | PAC | Control | P Between | | |
| **PAC vs No PAC** | | | | | | | | | | | | |
| Guyatt, 1991 (31) | M/SICU | 16 | 17 | 61 | 63 | All-cause | Net difference % | -10 | | NS | C | Moderate |
| Valentine, 1998 (7) | SICU | 60 | 58 | 64 | 100 | All-cause | % | 5 | 2 | NS | B | Narrow |
| Bonazzi, 2002 (30) | SICU | 50 | 50 | 67 | 100 | All-cause | % | 0 | 0 | NS | B | Narrow |
| Berlauk, 1991 (29) | SICU | 45[b] | 21 | 62 | 49 | All-cause | % | 2.2 | 9.5 | 0.08[d] | | Narrow |
| | | 23[c] | | | 70 | | | 0 | | | | |
| Harvey, 2005 (32) | MICU | 506 | 507 | 65 | 57 | Hospital | Adj HR | 1.09 | | | | |
| | | | | | | ICU | % | 60 | 57 | NS | A | Wide |
| | | | | | | 28 day | % | 62 | 60 | B | | |
| Sandham, 2003 (37) | SICU | 997 | 997 | 72 | 70 | Hospital | % | 7.8 | 7.7 | NS | A | Moderate |
| | | 930 | 963 | | | 6 month | % | 12.6 | 11.9 | NS | | |
| | | 910[68] | 941 | | | 12 month | % | 17.9 | 16 | NS | | |
| | | | | | | | Adj RR | 1.0 | | | | |
| Richard, 2003 (36) | ICU (mixed units) | 338 | 343 | 63 | 67 | 28 day | % | 59 | 61 | NS | A | Moderate |
| | | | | | | | Adj HR | 0.97 | | | | |
| | | | | | | | 14 day RR | 0.97 | | | | |
| | | 335 | 341 | | | | 90 day RR | 0.98 | | | | |
| ESCAPE, 2005 (14) | CCU | 206 | 207 | 56 | 74 | ~30 day | OR | 0.97 | | NS | A | Moderate |
| | | | | | | 180 day | | 1.26 | | | | |
| Rhodes, 2002 (35) | ICU | 96 | 105 | 68 Median | nd | 28 day | Adj OR | 0.96 | | NS | A | Wide |
| **PAC vs CVP** | | | | | | | | | | | | |
| Isaacson, 1990 (33) | SICU | 49 | 53 | 65 | nd | All-cause | No. | 1 | 0 | NS | B | Narrow |
| Shoemaker, 1988; 1990 (39;41) | SICU | 28[e] | 30 | 53 | 75 | All-cause | % | 4 | 23 | <0.1 | B | Narrow |
| | | 30[f] | | | 39 | | | 33 | | NS | | |
| Wheeler, 2006 NHLBI (15) | ICU | 513 | 487 | 49 | 45 | 60 day | % | 27.4 | 26.3 | NS | A | Narrow |
| | | | | | | | RR | 1.1 | | | | |
| Bender, 1997 (5) | SICU | 51 | 53 | 65 | 63 | All-cause | No. | 1 | 1 | NS | B | Narrow |
| Schultz, 1985 (38) | ICU | 35 | 35 | 78 | 28 | All-cause | % | 2.9 | 29 | <0.01 | C | Narrow |

[a] Values for the PAC group
[b] Group 1: PAC placement 12 hours before surgery[56]
[c] Group 2: PAC placement 3 hours before surgery
[d] 2 PAC arms vs Control
[e] PAC-Protocol: Supranormal therapeutic goals
[f] PAC-Control: Similar therapeutic goals for CVP and PAC groups

**Figure 1. Metaanalysis of odds ratio of death, PAC vs. control**




* Rhodes 2002 reported only an adjusted OR of death. Exclusion of this study does not affect summary estimates.

Random effects model metaanalyses of odds ratio (OR) of death comparing patients who received PAC monitoring to patients who did not receive PAC monitoring in critical care settings. Diamonds display metaanalysis results centered on pooled estimates and extending to 95% confidence interval (CI). Squares and lines indicate OR estimates and 95% CI for individual studies. The size of the boxes are proportional to the weight of each study in the overall metaanalysis. Studies are ordered by setting, then sample size.

Appl, applicability rated W (wide), M (moderate), N (narrow); CCU, coronary care unit; CI confidence interval; Ctrl, control; CVP, central venous pressure catheter; ICU, intensive care unit; MICU, medical intensive care unit; n, number of events (death); N, number of patients; OR, odds ratio; PAC, pulmonary artery catheter; Quality, methodological quality rated A (good), B (fair), C (poor); SICU, surgical intensive care unit.

## Length of Stay (Figures 2 & 3, Tables 4 & 5)

A total of 13 trials reported data on the length of hospital stay and/or on the length of ICU stay (5;7;14;15;29-31;33-37;39). Of these, Rhodes 2002 uniquely reported the median length of hospital and ICU stay and their confidence intervals were expressed as percent changes (35). Therefore, it was excluded in the metaanalyses of length of hospital or ICU stay. However, consistent with the other trials, Rhodes 2002 did not find any statistically significant difference in the length of hospital or ICU stay between patients received PAC monitoring and those who received no PAC monitoring (CVP allowed).

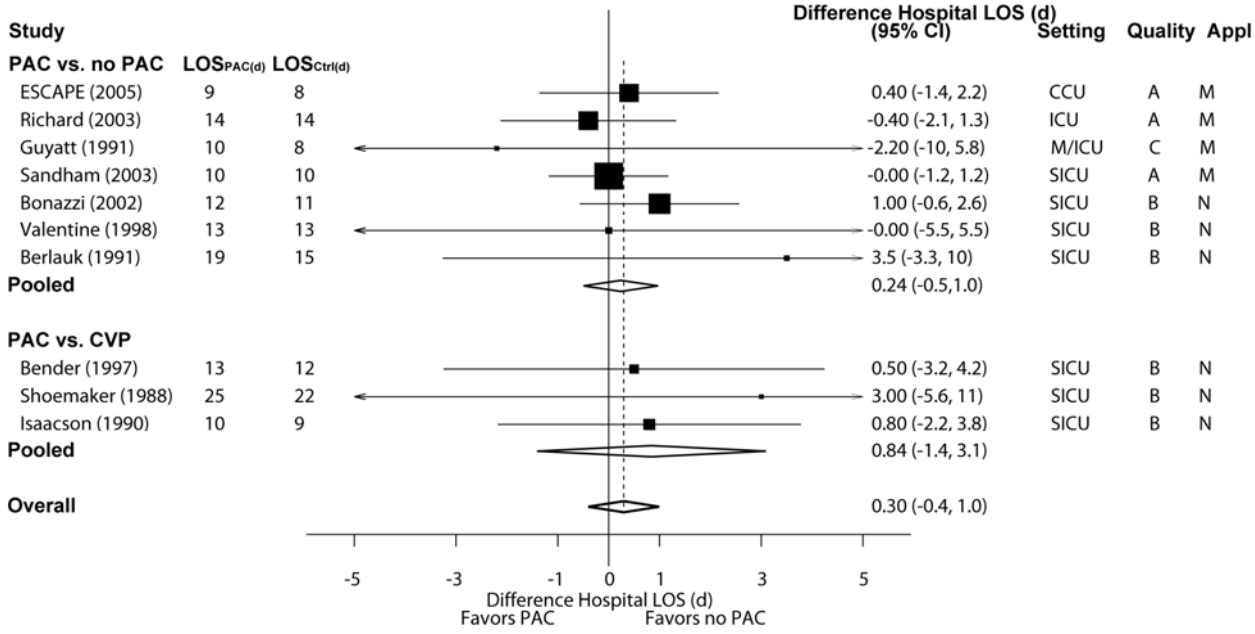
### Length of Hospital Stay (Figure 2, Table 4)

Ten trials reported data on the length of hospital stay in patients received PAC monitoring and in the control patients in critical care settings (5;7;14;29-31;33;36;37;39). Of these, seven compared length of hospital stay in patients who received PAC monitoring with

those who received no PAC monitoring (7;14;29-31;36;37) and three compared that with patients who received CVP monitoring (5;33;39). One study was in a CCU setting, one was in an ICU setting, one was in a M/SICU setting, and seven were in SICU settings. Three and seven studies were of good or moderate methodological quality (Grade A or B), respectively. Four studies were of moderate applicability, 6 narrow.

The mean lengths of hospital stay ranged from 9 to 25 days in the PAC monitoring groups and from 8 to 22 days in the control groups. The overall mean difference in the length of hospital stays was 0.30 (95% CI -0.40, 0.99) days between patients who received PAC monitoring and control patients who did not receive PAC monitoring in critical care settings. There was no statistically significant heterogeneity across the 10 studies. In the seven studies that compared PAC to no PAC monitoring, the random effects combined mean difference in the length of hospital stay was 0.24 (95% CI -0.50, 0.97) days. In the three studies that compared PAC to CVP monitoring, the random effects combined mean difference in the length of hospital stay was 0.84 (95% CI -1.41, 0.99) days. There was no statistically significant heterogeneity within each subgroup, and there was no statistically significant difference between the combined risk differences in the two groups (**Figure 2**).

**Figure 2. Metaanalyses of mean difference in hospital length of stay (LOS), PAC vs. control**




Random effects model metaanalyses of mean difference in hospital length of stay comparing patients who received PAC monitoring to patients who did not receive PAC monitoring in critical care settings. Diamonds display metaanalysis results centered on pooled estimates and extending to 95% confidence interval (CI). Squares and lines indicate estimates of means and 95% CI for individual studies. The size of the boxes are proportional to the weight of each study in the overall metaanalysis. Studies are ordered by setting, then sample size.

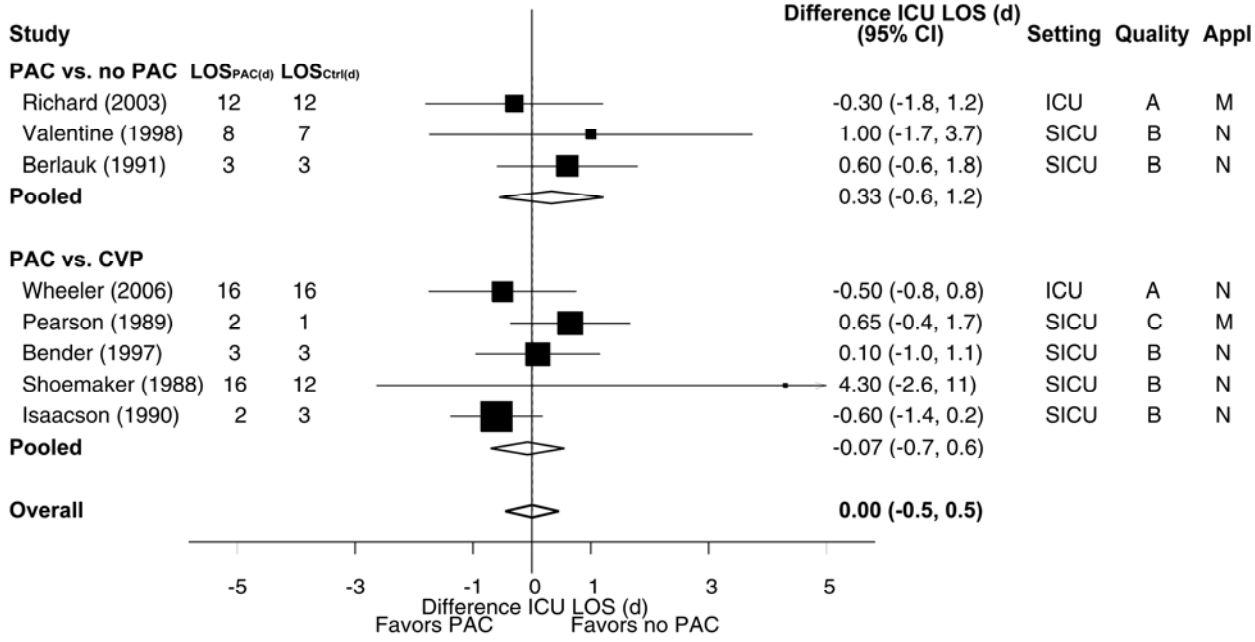
Appl, applicability rated W (wide), M (moderate), N (narrow); CCU, coronary care unit; CI confidence interval; Ctrl, control; CVP, central venous pressure catheter; d, days; ICU, intensive care unit; LOS, length of stay; MICU, medical intensive care unit; PAC, pulmonary artery catheter; Quality, methodological quality rated A (good), B (fair), C (poor); SICU, surgical intensive care unit.

**Length of ICU Stay (Figure 3, Table 5)**

A total of eight trials reported data on the length of ICU stay in patients who received PAC monitoring and in the control patients in critical care settings (5;7;15;29;33;34;36;39). Of these, three compared length of ICU stay in patients receiving PAC monitoring with those receiving no PAC monitoring (7;29;36) and five compared that to patients who received CVP monitoring (5;15;33;34;39). Two studies were in ICU settings and six were in the SICU settings. One and six studies were of good or moderate methodological quality (Grade A or B), respectively, and one was of poor quality (Grade C). Two were of moderate applicability, 6 narrow.

The mean lengths of ICU stay ranged from 2 to 16 days in the PAC monitoring groups and from 1 to 16 days in the control groups. The overall mean difference in the length of hospital stay was 0.00 (95% CI -0.45, 0.46) days between patients who received PAC monitoring and control patients who did not receive PAC monitoring in critical care settings. There was no statistically significant heterogeneity across the eight studies. In the four studies that compared PAC to no PAC monitoring, the random effects combined mean difference in the length of hospital stay was 0.33 (95% CI -0.56, 1.22) days. In the four studies that compared PAC to CVP monitoring, the random effects combined mean difference in the length of hospital stay was -0.07 (95%CI -0.70, 0.55) days. There was no statistically significant heterogeneity within each subgroup, and there was no statistically significant difference between the combined risk differences in the two groups. (**Figure 3**)

**Figure 3. Metaanalyses of mean difference in ICU length of stay, PAC vs. control**




Random effects model metaanalyses of mean difference in intensive care unit (ICU) length of stay comparing patients who received PAC monitoring to patients who did not receive PAC monitoring in critical care settings. Diamonds display metaanalysis results centered on pooled estimates and extending to 95% confidence interval (CI). Squares and lines indicate estimates of means and 95% CI for individual studies. The size of the boxes are proportional to the weight of each study in the overall metaanalysis. Studies are ordered by setting, then sample size.

CI confidence interval; Ctrl, control; CVP, central venous pressure catheter; d, days; ICU, intensive care unit; LOS, length of stay; PAC, pulmonary artery catheter.

**Table 4. Length of hospital stay in patients with PAC vs control in randomized controlled trials**

| Study, Year | Setting | No. Analyzed | | Mean Age (yr)[a] | % Male [a] | Sample | Metric/ Units | Results | | | Quality | Applicability |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | PAC | No PAC | | | | | PAC | No PAC | P between | | |
| **PAC vs No PAC** | | | | | | | | | | | | |
| Harvey, 2005 (32) | MICU | 506 | 508 | 65 | 57 | Survivors | days, median | 34 | 40 | NS | A | Wide |
| | | | | | | Non survivors | | 3 | 3 | NS | | |
| Rhodes, 2002 (35) | ICU | 96 | 105 | 68 median | nd | All | days, median | 13 | 14 | NS | A | Wide |
| | | | | | | Survivors | | 29 | 25 | NS | | |
| Sandham, 2003 (37) | SICU | 997 | 997 | 72 | 70 | Hospital | days, median | 10 | 10 | NS | A | Moderate |
| ESCAPE, 2005 (14) | CCU | 206 | 207 | 56 | 74 | All | HR | 1.04 | | NS | A | Moderate |
| Guyatt, 1991 (31) | MICU, SICU | 16 | 17 | 61 | 63 | All | Net difference, days | -2.2 | | NS | C | Moderate |
| Valentine, 1998 (7) | SICU | 60 | 58 | 64 | 100 | All | days | 13 | 13 | NS | B | Narrow |
| Berlauk, 1991 (29) | SICU | 45 [b] | 21 | 62 | 49 | All | days | 19.4 | 15.4 | NS | B | Narrow |
| | | 23 [c] | | | 70 | | | 18.0 | | | | |
| Bonazzi, 2002 (30) | SICU | 50 | 50 | 67 | 100 | All | days | 12 | 11 | NS | B | Narrow |
| **PAC vs CVP** | | | | | | | | | | | | |
| Isaacson, 1990 (33) | SICU | 49 | 53 | 65 | nd | All | days | 10.2 | 9.4 | NS | B | Narrow |
| Shoemaker, 1988; 1990 (39;41) | SICU | 28 [d] | 30 | 53 | 75 | All | days | 19.3 | 22.2 | NS | B | Narrow |
| | | 30 [e] | | | 39 | | | 25.2 | | | | |
| Bender, 1997 (5) | SICU | 51 | 53 | 65 | 63 | All | days | 12.5 | 12.0 | NS | B | Narrow |

CCU, coronary care unit; ICU, intensive care unit; HR, hazard ratio; MICU, medical intensive care unit; nd, no data; NS, non-significant; PAC, pulmonary artery catheter; SICU, surgical intensive care unit; vs, versus; yr, year; %, percentage

[a] Values for the PAC group
[b] Group 1: PAC placement 12 hours before surgery
[c] Group 2: PAC placement 3 hours before surgery
[d] PAC-Protocol: Supranormal therapeutic goals
[e] PAC-Control: Similar therapeutic goals for CVP and PAC groups

**Table 5. Length of intensive care unit (ICU) stay in patients with PAC vs control in randomized controlled trials**

| Study, Year | Setting | No. Analyzed | | Mean Age (yr)[a] | % Male [a] | Sample | Metric/ Units | Results | | P Between | Quality | Applicability |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | PAC | Control | | | | | PAC | Control | | | |
| **PAC vs No PAC** | | | | | | | | | | | | |
| Harvey, 2005 (32) | MICU | 506 | 508 | 65 | 57 | Survivors | days, median | 12.1 | 11.0 | NS | A | Wide |
| | | | | | | Non survivors | | 2.6 | 2.5 | NS | | |
| Rhodes, 2002 (35) | ICU | 96 | 105 | 68 median | nd | All | days, median | 5.7 | 4 | NS | A | Wide |
| | | | | | | Survivors | | 10 | 6 | NS | | |
| Valentine, 1998 (7) | SICU | 60 | 58 | 64 | 100 | All | days | 8 | 7 | NS | B | Narrow |
| Berlauk, 1991 (29) | SICU | 45 [b] | 21 | | 49 | All | days | 3.5 | 2.6 | NS | B | Narrow |
| | | 23 [c] | | 62 | 70 | | | 2.5 | | | | |
| **PAC vs CVP** | | | | | | | | | | | | |
| Wheeler 2006 (15) | ICU | 513 | 487 | 49 | 45 | All | ICU-free day, at day 28 | 12.0 | 12.5 | NS | A | Narrow |
| Isaacson, 1990 (33) | SICU | 49 | 53 | 65 | nd | All | days | 2.1 | 2.7 | NS | B | Narrow |
| Shoemaker, 1988; 1990 (39;41) | SICU | 28 [d] | 30 | 56 | 75 | All | days | 10.2 | 11.5 | NS | B | Narrow |
| | | 30 [e]68 | | 53 | 39 | | | 15.8 | | | | |
| Bender, 1997 (5) | SICU | 51 | 53 | 65 | 63 | All | days | 2.7 | 2.6 | NS | B | Narrow |
| Pearson, 1998 (34) | SICU | 86 | 26 | nd | nd | All | days | 1.6 | 1.35 | NS | C | Moderate |
| | | 33 [f] | | | | | | 2.8 | | | | |

ICU, intensive care unit; MICU, medical intensive care unit; nd, no data; NS, non-significant; PAC, pulmonary artery catheter; SICU, surgical intensive care unit; vs, versus; yr, year; %, percentage.

[a] Values for the PAC group
[b] Group 1: PAC placement 12 hours before surgery
[c] Group 2: PAC placement 3 hours before surgery
[d] PAC-Protocol: Supranormal therapeutic goals
[e] PAC-Control: Similar therapeutic goals for CVP and PAC groups
[f] Reassigned to PAC group

## Medical morbidities (Tables 6 & 7)

Eleven trials reported comparative rates of various medical morbidities between patients with PAC and either no PAC or CVP (5;7;14;15;29;30;33;35;37;39-41). The medical morbidities included "overall," cardiovascular, pulmonary, renal, infection, hepatic, graft thrombosis, and gastrointestinal, but do not include adverse events related to PAC use. Across studies and morbidities, only the ESCAPE trial reported a statistically significant difference in morbidity event rates, such that at least one morbidity occurred in about twice as many patients who had PAC than who did not have PAC (14). In all the studies, where event rates differed, the number of events that occurred more commonly without PAC was equal to the number of events that were more common with PAC. The total rates of any event reported among patients with and without PAC were roughly equal such that in both groups, overall, about 1 event was reported per 3 patients investigated.

### Overall (Table 6)

Five studies reported some variation of total number of medical morbidities. As noted, only the ESCAPE trial found a significant difference based on intervention, favoring no PAC. Valentine 1998 also found a somewhat higher rate of postoperative medical morbidity in those with PAC. In contrast, Berlauk 1991 and Shoemaker 1988/1990 found substantially higher medical morbidity rates in those who did not receive PAC. Shoemaker1988/1990 was actually designed to compare an active protocol based on PAC with both a CVP control and a PAC control (without the active protocol). While similar rates of events occurred in the PAC and PAC "control" arms, the 28 patients in the PAC protocol arm had only one organ failure (respiratory), a significantly lower rate of events than the controls. The final study, Bender 1997, found equal rates of events.

### Cardiovascular (Table 6)

Nine trials reported rates of cardiovascular events. None reported statistically significant differences in rates of various events, including myocardial infarction, congestive heart failure, pulmonary edema, cardiogenic shock, cardiac arrest, stroke, and overall cardiac events. There was no consistent finding of either patients with or without PAC having fewer cardiovascular events.

### Pulmonary (Table 6)

Among the five studies that reported pulmonary events, three found no substantial differences in event rates and the two others came had opposite findings about whether specific respiratory events were more common with or without PAC. The pulmonary morbidities reported were respiratory failure, pulmonary effusion, acute respiratory distress syndrome, and overall pulmonary events.

### Renal (Table 7)

Ten studies reported on kidney injury, including need for renal replacement therapy. The studies were evenly distributed among those that found higher rates of renal events with or without PAC, or that found no difference in rates.

**Infectious disease (Table 7)**

Only clinically significant infections likely related to the patients' underlying medical or surgical diseases are included here. Studies that reported only infections that were deemed to be related to PAC are discussed under Question 4 on adverse events related to PAC. Studies that reported wound infections, bacteremia (alone), or other relatively minor infections were not included.

Four studies reported rates of either pneumonia, sepsis or septic shock, or general infection. The ESCAPE trial did not define what was meant by "infection," except that these did not include PAC-related infections; but this trial was included nonetheless. Consistent with their findings for other medical morbidities, ESCAPE found somewhat higher rates of infection with PAC, Shoemaker 1988/1990 found a somewhat higher rate of sepsis without PAC, and the other two trials found similar rates of either pneumonia or sepsis, regardless of PAC.

**Miscellaneous medical morbidities (Table 7)**

Other clinically important medical morbidities that were evaluated were hepatic insufficiency or failure, gastrointestinal events, and graft thrombosis (after peripheral vascular disease surgery). These were evaluated by six studies. No consistent relative event rates were found across studies.

**Table 6. Reports of medical morbidities (overall, cardiovascular, and pulmonary events) in randomized trials. See Tables 11, 12, and 15 for cardiovascular and pulmonary complications attributable to PAC.**

| | N | | Overall | | | | Cardiovascular | | | | Pulmonary | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **PAC** | **Control** | **Outcome** | **PAC** | **Control** | **P** | **Outcome** | **PAC** | **Control** | **P** | **Outcome** | **PAC** | **Control** | **P** |
| **Sandham (37)** | 997 | 997 | | | | | Myocardial infarction | 4% | 3% | NS | | | | |
| | | | | | | | CHF | 13% | 11% | NS | | | | |
| **Wheeler NHLBI (15)** | 513 | 487 | | | | | | | | | | | | |
| **ESCAPE (14)** | 215 | 218 | ≥1 event [a] | **21.9%** | 11.5% | **.04** | Cardiogenic shock | 0.5% | **0.9%** | NS | | | | |
| | | | ≥1 event [b] | **20%** | 11.5% | nd | Ischemia/angina | **4.2%** | 1.8% | NS | | | | |
| | | | | | | | Myocardial infarction | 0% | **0.5%** | NS | | | | |
| | | | | | | | Stroke/TIA | **0.5%** | 0% | NS | | | | |
| | | | | | | | Cardiac arrest | **4.2%** | 2.3% | NS | | | | |
| **Rhodes (35)** | 96 | 105 | | | | | | | | | ARDS | ≥14% [c] | ≥17% [c] | NS |
| **Berlauk (29)** | 66 | 21 | All | 17% | **43%** | nd | Overall | 11% | **24%** | nd | Overall | 0% | 0% | |
| | | | | | | | CHF | 6% | 5% | nd | | | | |
| | | | | | | | Myocardial infarction | 5% | **14%** | nd | | | | |
| **Valentine (7)** | 60 | 60 | Post-operative | **25%** | 17% | NS | Overall | **15%** | 7% | NS | Overall | **12%** | 9% | NS |
| | | | | | | | Stroke | 0% | 0% | | | | | |
| **Shoemaker (39;41)** | 58 | 30 | Organ failure | 55% | **73%** | nd | Myocardial infarction | **3%** | 0% | nd | Respiratory failure | 17% | **23%** | nd |
| | | | Overall | 0.9/pt | 1.0/pt | nd | Pulmonary edema | **9%** | 0% | nd | Pulmonary effusion | 10% | 7% | nd |
| **Bender (5)** | 51 | 53 | All | 14% | 13% | nd | Myocardial infarction | 6% | **9%** | nd | | | | |
| | | | | | | | Pulmonary edema | **4%** | 2% | nd | | | | |
| **Bonazzi (30)** | 50 | 50 | | | | | Overall | 4% | 4% | NS | | | | |
| **Isaacson (33)** | 49 | 53 | | | | | Myocardial infarction / cardiogenic shock | 2% | 2% | nd | Pulmonary effusion | 2% | 2% | nd |
| | | | | | | | Pulmonary edema | 2% | 2% | nd | | | | |
| **Joyce (40)** | 21 | 19 | | | | | Overall | 0 | 0 | | | | | |

**Percentages in bold were "substantially" larger than other arm (though generally nonsignificantly so).**

ARDS, acute respiratory distress syndrome; CHF, congestive heart failure; nd, no data; NS, statistically nonsignificant; PAC, pulmonary artery catheter; pt, (events per) patient; TIA, transient ischemic attack.

[a] including PAC infection (4 v 0 events)

[b] without PAC infection (assuming no other events occurred in these patients)

[c] Number (and %) of patients with outcomes reported and statistical analyses on a daily basis for 0-5 days. These values represent the maximum percentage of patients on any given day. It is possible that a larger percentage of patients had the condition at some time during the 5 days. The statistical analyses are only for daily rates.

**Table 7. Reports of medical morbidities (renal, infection, hepatic, graft thrombosis, and gastrointestinal events) in randomized trials. See Table 14 for infectious complications attributable to PAC**

| | N | | Renal | | | | Infection | | | | Other | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **PAC** | **Control** | **Outcome** | **PAC** | **Control** | **P** | **Outcome** | **PAC** | **Control** | **P** | **Outcome** | **PAC** | **Control** | **P** |
| **Sandham (37)** | 997 | 997 | Renal insufficiency | 7.4% | **9.8%** | .07 | Pneumonia | 6.7% | 7.3% | NS | Hepatic insufficiency | 2.4% | 2.7% | NS |
| **Wheeler NHLBI (15)** | 513 | 487 | Renal replacement | 14% | 11% | NS | | | | | | | | |
| **ESCAPE (14)** | 215 | 218 | SCr | worsened less with PAC | | nd | Infection | **13%** | 9% | NS | | | | |
| **Rhodes (35)** | 96 | 105 | Renal failure | **≥35%** [a] | ≥21% [a] | NS [a] | | | | | | | | |
| **Berlauk (29)** | 66 | 21 | Renal failure | 2% | **5%** | nd | | | | | Graft thrombosis | 3% | **19%** | nd |
| **Valentine (7)** | 60 | 60 | Overall | **7%** | 2% | NS | | | | | Graft thrombosis | 0% | 0% | |
| **Shoemaker (39;41)** | 58 | 30 | Renal failure | 12% | **23%** | nd | Sepsis | 16% | **20%** | nd | Hepatic failure | 3% | **7%** | nd |
| **Bender (5)** | 51 | 53 | | | | | Sepsis | 4% | 4% | | Graft thrombosis | 2% | 2% | nd |
| **Bonazzi (30)** | 50 | 50 | Renal failure | 0 | 0 | | | | | | | | | |
| **Isaacson (33)** | 49 | 53 | Renal injury | **4%** | 2% | nd | | | | | Gastro-intestinal | 2% | **6%** | nd |
| **Joyce (40)** | 21 | 19 | Renal failure | 0 | 0 | | | | | | | | | |

**Percentages in bold were "substantially" larger than other arm (though generally nonsignificantly so).**
nd, no data; NS, statistically nonsignificant; PAC, pulmonary artery catheter; SCr, serum creatinine.

[a] Number (and %) of patients with outcomes reported and statistical analyses on a daily basis for 0-5 days. These values represent the maximum percentage of patients on any given day. It is possible that a larger percentage of patients had the condition at some time during the 5 days. The statistical analyses are only for daily rates.

## Duration of ventilation (Table 8)

Three trials reported on differences in duration of mechanical ventilation in patients with either PAC or CVP monitoring (7;15;39;41). All three trials found no statistically significant difference in mean duration of time that patients required mechanical ventilation. A relatively large trial of 1000 patients in the ICU (Wheeler 2006) found similar numbers of ventilator-free days. Two smaller surgical ICU-based trials of 58 patients (Shoemaker 1988/1990) and 118 patients (Valentine 1998) found no significant differences in time on ventilation. Valentine did find a much greater duration of ventilation in those with PAC, but the variance of the duration of ventilation among the PAC group was so large that our estimated 95% confidence interval for the difference between the two arms is –2 hours (favoring no PAC) to +72 hours.

## Quality of life and disease severity scores (Table 9)

Four trials evaluated different measures of quality of life (or disease severity). In total, the studies compared 377 patients who had PAC used and 380 without PAC (14;30;31;35). Two were deemed to be of good quality and two fair quality. The trials varied in applicability from narrow to wide and each study evaluated patients in different settings.

The ESCAPE trial reported that the Minnesota Living with Heart Failure questionnaire improved in both groups by 1 month, with greater improvement in the PAC group, but that by 6 months the control group matched the PAC group. No further data were reported. They found no differences in changes in either a global symptom score or an orthopnea score (both of which improved equally in both groups of patients).

In a relatively small study of only 33 randomized patients, Guyatt 1991 found that changes in (baseline-adjusted) modified APACHE scores were statistically significantly worse after PAC use than without PAC at discharge from the intensive care unit. However, the two studies that evaluated the Systemic Organ Failure Assessment (SOFA) score found no differences between interventions.

## Optimization of treatment

No study that met eligibility criteria reported data on maximization of ACE inhibitor dose or other types of treatment optimization.

**Table 8. Duration of ventilation in patients with PAC vs control in randomized controlled trials**

| Study, Year | Setting | No. Analyzed | | Mean Age (yr) [a] | % Male [a] | Outcome | Results | | | | Quality | Applicability |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | PAC | Control | | | | Metric/ Units | PAC | Control | P Between | | |
| **PAC vs No PAC** | | | | | | | | | | | | |
| Valentine, 1998 (7) | SICU | 60 | 58 | 64 | 100 | Ventilation | hours | 35 | 6 | NS | B | Narrow |
| **PAC vs CVP** | | | | | | | | | | | | |
| Wheeler 2006 (15) | ICU | 513 | 487 | 49 | 45 | Ventilator-free days, day 28 | days | 13.2 | 13.5 | NS | A | Narrow |
| Shoemaker, 1988; 1990 (39;41) | SICU | 28 [b]<br>30 [c] | 30 | 53 | 75<br>39 | Duration of ventilation | days | 2.3<br>9.4 | 4.6 | NS | B | Narrow |

ICU, intensive care unit; MICU, medical intensive care unit; nd, no data; No., number; NS, non-significant; PAC, pulmonary artery catheter; SICU, surgical intensive care unit; SOFA, vs, versus; yr, year; %, percentage.

[a] Values for the PAC group
[b] PAC-Protocol: Supranormal therapeutic goals
[c] PAC-Control: Similar therapeutic goals for CVP and PAC groups

**Table 9. Quality of life or symptom score in patients with PAC vs control in randomized controlled trials**

| Study, Year | QOL/ symptom | Setting | No. Analyzed | | Mean Age (yr) [a] | % Male [a] | Baseline Score[1] | Metric / Units (Score Range) | Results | | | Quality | Applicability |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | PAC | No PAC | | | | | PAC | No PAC | P Between | | |
| **PAC vs No PAC** | | | | | | | | | | | | | |
| Bonazzi, 2002 (30) | SOFA 2nd postop. day | SICU | 50 | 50 | 67 | 100 | 10 [b] | Score (24 max, lower=better) | 8 | 8 | NS | B | Narrow |
| ESCAPE, 2005 (14) | Symptom score (global) | CCU | 215 | 208 | 56 | 74 | 43 | Score (?100 max, implied higher=better) | +25 | +24 | NS | A | Moderate |
| | Minnesota Living with Heart Failure questionnaire | | | | | | nd | nd | PAC better than No PAC at 1 month, but not 6 months | | | | |
| | Orthopnea score | | | | | | 3.3 | Score (0-4) | -1.4 | -1.2 | NS | | |
| Guyatt, 1991 (31) | Lowest modified APACHE | MICU, SICU | 16 | 17 | 61 | 63 | | Final Score, adjusted for baseline | | 7.0 | .03 (favoring No PAC) | B | Moderate |
| | Mean modified APACHE | | | | | | | | 14.4 | 11.1 | .04 (favoring No PAC) | | |
| Rhodes, 2002 (35) | SOFA scores, 0-5 d change | ICU | 96 | 105 | 68 median | nd | 7 median | Score (24 max, lower=better) | -3 | -4 | NS | A | Wide |

APACHE, Acute Physiology And Chronic Health Evaluation; CCU, cardiac care unit; ICU, intensive care unit; MICU, medical intensive care unit; nd, no data; No., number; NS, non-significant; PAC, pulmonary artery catheter; SICU, surgical intensive care unit; SOFA, Systemic Organ Failure Assessment; vs, versus; yr, year; %, percentage.

10.8

[a] Values for the PAC group
[b] 6 hours after surgery

**Question 4:** What complications and adverse events associated with pulmonary artery catheter monitoring have been reported?

## Summary of review articles on PAC complications

To complement the systematic review of PAC complications among RCTs and larger cohort studies, we collected information from various more comprehensive reviews (both systematic and narrative) of PAC complications. The review articles commonly divide complications temporally according to the (a) insertion, (b) management, and (c) removal of the PACs. A list of reported complications associated with each period is shown in **Table 10**.

**Table 10. Complications associated with pulmonary artery catheters**

| Insertion | Maintenance | Removal |
|---|---|---|
| Pneumothorax | Infection | Hemorrhage |
| Hemothorax / hemomediastinum | Bacteremia | Air embolism |
| Hematoma / hemorrhage | Candidemia | Arrhythmia |
| Accidental arterial puncture | Sepsis | Cardiovascular damage |
| Arrhythmia | Local infection | Vascular |
| Anaphylaxis (latex allergy) | Lung abscess / empyema | Valvular |
| Cardiovascular damage | Endocarditis | Cardiac wall |
| Vascular | Embolism | Catheter shear |
| Valvular | Air | |
| Cardiac wall | Thrombus | |
| Air embolism | Catheter / balloon | |
| Guide wire loss or fragmentation | Pulmonary infarct | |
| | Arrhythmia | |
| | Hemorrhage | |
| | Vascular / cardiac rupture / damage | |
| | Vessel thrombosis | |

## Complications associated with PAC insertion

Kelso et al. performed a systematic review of articles that primarily described complications associated with PAC use from 1979 to 1996 (43). A variety of complications, including most events listed in Table 10, are discussed. However, evidence on event rates were described only for a few outcomes. Most studies were retrospective in design and many included relatively few individuals. No attempts at metaanalysis were performed. The best estimate of cardiac arrhythmias requiring treatment was ≤3 percent (44). It was noted that complete heart block was rare, most commonly occurring in patients with left bundle branch block, potentially fatal, but the incidence is unknown.

In an issue-length review of complications of invasive hemodynamic monitoring in the intensive care unit from 1988, Sladen describes and provides opinions on a wide range of complications, but includes only occasional estimates of event rates. Among those highlighted are risks of pneumothorax (1.4 percent) and arterial puncture (7.7 percent) during central venous access (45). Both of these estimates are from a 1986 report of 142 patients (46).

None of the reviews discussed loss of the guidewire into patient during insertion, though this is one of the primary complications taught to medical personnel during training. This complication may have been the cause of several of the described complications including

cardiac arrhythmias, major artery and vein rupture, pulmonary embolism, pneumothorax, and thrombosis.

## Complications associated with PAC maintenance

The most commonly described complications described that occur while the PAC is being left in place and used for hemodynamic monitoring are infections, pulmonary artery and right ventricular damage**,** and pulmonary infarction. Kelso et al. reported several estimates of rates of infections including bacteremia in 1-6 percent of patients and local infections in 19 percent (43). In an extensive review of infectious complications of PACs from 1994, Mermel and Maki (47) describe infectious endocarditis occurring in less than 2 percent of patients (by autopsy). Other infectious complications described include septic thrombosis (infected thrombus surrounding the catheter), septic pulmonary emboli, bacteremia, candidemia, pulmonary artery mycotic aneurysm, parenchymal lung abscess and empyema. However, they note that while many prospective studies of risk have been published, few used unambiguous criteria for catheter-related bloodstream infections and several of these were small or did not report complete analyses. From 14 prospective studies with at least 75 catheters, reported between 1979 and approximately 1993, it was estimated that 0-4.6 percent of catheters produce bacteremia or candidemia (median 1.0 percent) and there were 0-13.2 (median 4.8) cases of bacteremia or candidemia per 1000 catheter-days. They note though that these reports "May underestimate the true incidence of PAC-related bloodstream infection because it is not clear in most of the reported studies whether a proactive effort was made by the investigators to assure that blood cultures were done in every patient with fever or other signs of sepsis" (47).

Kelso et al. report a range of rates of pulmonary artery rupture or aneurysm from 0.03-0.2 percent, with mortality of 45-65 percent across various studies (43). Liu and Webb, in introductory material for their analysis of reported PAC-related deaths, note pulmonary artery rupture rates between 0.016 and 1.0 percent, with a mortality rate above 50 percent (48). Kelso et al. also give a series of rare events described in case reports and series, including right ventricle perforation, air embolism, thrombosis formation, catheter fragment embolization, and pulmonary infarct.

Notably, they categorize "inappropriate treatment of a patient based upon inaccurate hemodynamic measurements" as a complication. They note two studies of practitioner knowledge of PAC (49;50). Among almost 500 North American physicians, the mean multiple-choice test score was 67 percent correct (49). A slightly revised version of the test was given to two groups of American nurses who scored about 50 percent correct (50).

## Complications associated with PAC removal

The adverse events that have been described to occur at PAC removal include catheter knotting, arrhythmias, catheter shear (tearing), and structural damage. These have been reported in case reports (43). Karanikas et al. report on a systematic review of case reports of catheter knotting (51). They found reports of 53 PAC catheter knots between 1950 and 2000 (they also report on knots in other catheters). Almost 60 percent were successfully removed using interventional radiological techniques, but one-third required surgery. Four catheter knots were left *in situ*. However six of the reported cases (8 percent) died as a direct result of the catheter knot.

### Death

Liu and Webb (48) performed an analysis of the manufacturer and user facility device experience database gathered by the Food and Drug Administration (FDA). Between 1993 and 1999 48 deaths associated with PAC were reported to the FDA. Of these, 42 (88 percent) were due to pulmonary artery rupture, 2 were due to air embolism, 1 each were due to pleural cavity perforation and cardiac tamponade, and 2 were due to other causes. However, no estimate of a denominator or the reporting rate were made.

## Systematic review of PAC complications

Eighteen studies met our eligibility criteria for review of PAC complications (5;7;14;15;29;30;32;35-37;39;40;52-57). These included 12 of the randomized trials eligible for Key Question 3 (with a total of 3,017 patients who received PAC), 3 prospective cohort studies with at least 500 patients with PAC (6,986 patients total), and 3 retrospective analyses with at least 500 patients with PAC (39,187 patients total).

With the possible exception of the adverse events reported in the retrospective study of 32,442 patients (55), the event rates we summarized are likely to be high estimates of the true rates. This is so because for each adverse event we have included only those studies that explicitly report rates of the adverse event. We did not assume that lack of reporting meant that no adverse events (including death) occurred. Though relatively common adverse events may have been omitted by some authors, we consider it more likely that adverse events that were rare or did not occur in a particular sample of patients were more likely to be omitted.

From the RCTs, we attempted to extract equivalent adverse event data from both the PAC and the control arms under the assumption that some of the PAC-attributed "complications" (eg, ventricular arrhythmia, sepsis) may not in fact have been related to PAC placement or may have equally occurred due to CVP or other line placement. However, this approach was limited because no study reported the number of relevant events specifically in patients who had CVPs and many comparative studies reported these events only among patients with PAC. Nevertheless, three RCTs reported complication data. These data are presented in Tables 11-15, along with statistical significance of relative event rates.

### Arrhythmia (Table 11)

Nine studies with 13,122 patients reported event rates of various clinically significant arrhythmias (not including transient arrhythmias not requiring treatment). Five studies with 8645 patients reported on different potentially severe arrhythmias, or those requiring treatment, each finding event rates of approximately 3 percent. Ventricular tachycardia was explicitly reported by five studies of 5782 patients (one of which also reported on severe arrhythmias) and found in approximately 0.2 percent across studies; although a wide range, from 0.04 to 1.5 percent among the studies, possibly suggesting that different definitions of ventricular tachycardia were used or that the underlying risk of the event differed in the different study populations with different medical and surgical conditions. Notably, the rate of ventricular tachycardia was the same in the one RCT that reported rates in both arms (PAC and standard of care, where CVP was allowed) (37).

## Pneumothorax and hemothorax (Table 12)

Eight studies with 9714 patients reported rates of pneumothorax related to PAC use; three of these studies and a fourth study also reported on hemothorax rates in 2282 patients with PAC. Among these studies pneumothorax rates varied between 0 and 2 percent and hemothorax rates between 0.2 and 0.6 percent. Overall, about 1 in 200 patients evaluated experienced a pneumothorax and 1 in 325 patients a hemothorax related to PAC use. If we assume that no pneumothoraces or hemothoraces occurred in studies that reported only one of the events, then the overall rate of pneumothoraces remains the same at about 1 in 200 (0.5 percent), but drops to about 1 in 1500 (0.07 percent) for hemothoraces. Notably, the rates of hemothorax and pneumothorax were lower or the same in three RCTs (29;35;37).

## Major bleeding events (Table 13)

Nine studies with 45,507 patients reported rates of major artery punctures and pulmonary hemorrhage, though 32,442 patients were from one retrospective analysis of patients receiving PACs either in the operating room or the intensive care unit. Carotid artery punctures were relatively common, occurring in approximately 2.4 percent of patients in four studies (range 1.5 to 4.8 percent). Pulmonary artery rupture was reported by the large retrospective study, for which this was the primary outcome of interest, and relatively large prospective study. The two studies found broadly similar rates of 0.03 and 0.07 percent, respectively. Among four studies with 7901 patients, pulmonary hemorrhage (or infarction) occurred in approximately 1 in 800 patients, overall (range 0.06 and 0.9 percent). In one RCT, the rate of arterial punctures and of pulmonary hemorrhage was similar in both arms (37).

## Infections (Table 14)

Six studies with 2571 patients receiving PAC reported on clinically significant infections related to PAC use. We did not include reports of superficial or other wound infections that required only topical care. We attempted to exclude reports of positive blood cultures that either were not reported to have any clinical impact or that cleared with PAC removal. It is likely though that we misclassified the clinical importance of the septic events that were reported by the various studies. Among the five studies that appeared to be reporting on clinically important septicemia, this outcome occurred in approximately 1.6 percent of 2356 patients. Notably, though, among the larger studies (500 or more patients) about 1 percent of patients had septicemia, while the rate was 3 percent in each of the smaller studies. The rate of sepsis was the same in the one RCT that reported rates in both the PAC and usual care (some with CVP) arms (37). Two studies reported either that 1 percent of patients had septicemia or other infections (not including local infections) and that 2 percent had "PAC related infections." One study of 500 patients reported no cases of endocarditis. This outcome was not reported by other studies.

## Embolism (Table 15)

Four studies with 2296 patients reported rates of pulmonary embolism. Across studies about 0.5 percent of patients suffered a pulmonary embolism; though rates in the individual studies ranged from 0 to almost 1 percent. One of these studies reported that 1 patient among 941 who received PAC had a pulmonary infarction. A separate study reported that among 513 patients, 2 patients (0.6 percent) had air embolisms. Sandham 2003 found statistically significantly more pulmonary emboli among patients who had PACs (8/941, 0.9 percent) than

who had standard care, some of whom had CVPs (0/965, P=0.004) (37). The rates of pulmonary infarctions, though were equivalently low.

## Catheter knotting (Table 16)

Three studies reported rates of catheter knotting. The large prospective cohort study of 2860 patients in surgical intensive care units found a very low rate of 0.03 percent (1 patient), while the two smaller randomized trials found rates of about 1 to 2 percent (8 patients among 557 patients total). The reason for the discrepancy is unclear; although it is possible that different definitions of knotting were used, possibly including simple catheter looping within the right ventricle. Alternatively, poorer technique may have been used in the randomized trials in medical units than the cohort in surgical units, or that the event was underreported in the surgical units.

## Death (Table 17)

Among nine studies with 7769 patients, only 1 death (0.01 percent) related to PAC use was reported. The death occurred in the largest study (a retrospective cohort). The death was due to accidental overinflation of the balloon while measuring PAOP which resulted in massive pulmonary hemorrhage. If it can be assumed that no other deaths related to PAC occurred in the other studies that reported adverse events (omitting the evaluation of pulmonary rupture (55) in 32,422 patients) then the PAC-death rate was 1 in 16,748 or 0.006 percent.

**Table 11. Incidence of clinically significant arrhythmias in patients with PAC (or control, in parentheses). See Table 6 for data from RCTs on other, non-PAC-attributed cardiovascular outcomes.**

| Author | Year | Adverse Event | Setting | No. Analyzed | Mean Age (yr) | Male (%) | % with Adverse Event | Quality | Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Shah (57) | 1984 | Persistent PVCs requiring treatment | nd | 6245 | 62 | nd | 3.1 | C | Moderate |
| Damen (54) | 1986 | Ventricular fibrillation | Cardiac ICU | 1305 | nd | nd | 3 | B | Narrow |
| Wheeler (15) | 2006 | Ventricular arrhythmia | ICU | 513 | 49 | 45 | 3.7 | A | Narrow |
| Harvey (32) | 2005 | Arrhythmia requiring treatment | Medical ICU | 486 | 65 | 57 | 3 | A | Wide |
| Rhodes (35) | 2002 | Dysrhythmia, severe | General ICU | 96 | 68 | nd | 3 | A | Wide |
| Wheeler (15) | 2006 | Conduction defect | ICU | 513 | 49 | 45 | 1.0 | A | Narrow |
| Shah (57) | 1984 | LBBB resulting in complete heart block | nd | 6245 [113 [a]] | 62 | nd | 0.02 [0.9% [a]] | C | Moderate |
| Lopez-Sendon (56) | 1990 | Ventricular tachycardia | Coronary care unit | 2821 | 60 | 83 | 0.04 | B | Narrow |
| Damen (54) | 1986 | Ventricular tachycardia | Cardiac ICU | 1305 | nd | nd | 0.2 | B | Narrow |
| Sandham (37) | 2003 | Ventricular tachycardia | Surgical ICU | 941 (965) | 72 | 70 | 0.2 (0.2) NS | A | Moderate |
| Boyd (53) | 1983 | Ventricular tachycardia | All | 500 | nd | nd | 1.5 | B | Narrow |
| ESCAPE (14) investigators | 2005 | Ventricular tachycardia | Cardiac ICU | 215 | 46 | 74 | 0.5 | A | Moderate |
| *Total* | | *Ventricular tachycardia* | | *5782* | | | *0.2%* [b] | | |

ICU, intensive care unit; LBBB, left bundle branch block; nd, no data; PAC, pulmonary artery catheter; PVC, premature ventricular contractions.

[a] Patients with pre-existing LBBB

[b] Simple pooled (averaged) estimate. I.e., weighted only by sample size. All summary percentages are likely to be overestimates since studies without events that did not explicitly report no events are not included.

**Table 12. Incidence of hemothorax and pneumothorax in patients with PAC (or control, in parentheses). See Table 6 for data from RCTs on other, non-PAC-attributed pulmonary outcomes.**

| Author | Year | Adverse Event | Setting | No. Analyzed | Mean Age (yr) | Male (%) | % with Adverse Event | Quality | Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Sandham (37) | 2003 | Hemothorax | Surgical ICU | 941 (965) | 72 | 70 | 0.2 (0) NS | A | Moderate |
| Wheeler (15) | 2006 | Hemothorax | ICU | 513 | 49 | 45 | 0.6 | A | Narrow |
| Harvey (32) | 2005 | Hemothorax | Medical ICU | 486 | 65 | 57 | 0.2 | A | Wide |
| Richard (36) | 2003 | Hemothorax | ICU (mixed units) | 342 | 62 | 67 | 0.3 | B | Moderate |
| *Total* | | *Hemothorax* | | *2282* | | | *0.3%* [a] | | |
| Shah (57) | 1984 | Pneumothorax | nd | 6245 | 62 | nd | 0.5 | C | Moderate |
| Damen (54) | 1986 | Pneumothorax | Cardiac ICU | 1305 | nd | nd | 0.1 | B | Narrow |
| Sandham (37) | 2003 | Pneumothorax | Surgical ICU | 941 (965) | 72 | 70 | 0.9 (0.4) NS | A | Moderate |
| Wheeler (15) | 2006 | Pneumothorax | ICU | 513 | 49 | 45 | 1.2 | A | Narrow |
| Harvey (32) | 2005 | Pneumothorax | Medical ICU | 486 | 65 | 57 | 0 | A | Wide |
| Rhodes (35) | 2002 | Pneumothorax | General ICU | 96 (105) | 68 | nd | 0 (0) | A | Wide |
| Berlauk (29) | 1991 | Pneumothorax | Surgical ICU | 68 (21) | 66 | 56 | 1.5 (0) NS | B | Narrow |
| Valentine (7) | 1998 | Pneumothorax | Surgical ICU | 60 | 64 | 100 | 2 | B | Narrow |
| *Total* | | *Pneumothorax* | | *9714* | | | *0.5%* [a] | | |

ICU, intensive care unit; nd, no data; PAC, pulmonary artery catheter.

[a] Simple pooled (averaged) estimate. I.e., weighted only by sample size. All summary percentages are likely to be overestimates since studies without events that did not explicitly report no events are not included.

**Table 13. Incidence of major bleeding events in patients with PAC (or control, in parentheses)**

| Author | Year | Adverse Event | Setting | No. Analyzed | Mean Age (yr) | Male (%) | % with Adverse Event | Quality | Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Sandham (37) | 2003 | Arterial puncture | Surgical ICU | 941 (965) | 72 | 70 | 0.3 (0.1) NS | A | Moderate |
| Wheeler (15) | 2006 | Arterial puncture | ICU | 513 | 49 | 45 | 0.6 | A | Narrow |
| Shah (57) | 1984 | Carotid artery puncture | nd | 6245 | 62 | nd | 1.9 | C | Moderate |
| Damen (54) | 1986 | Carotid artery puncture | Cardiac ICU | 1305 | nd | nd | 4.8 | B | Narrow |
| Boyd (53) | 1983 | Carotid artery puncture | All | 500 | nd | nd | 1.5 | B | Narrow |
| Harvey (32) | 2005 | Carotid artery puncture | Medical ICU | 486 | 65 | 57 | 3 | A | Wide |
| *Total* | | *Carotid artery puncture* | | *8536* | | | *2.4%* [a] | | |
| Kearney (55) | 1995 | Pulmonary artery rupture | OR & ICU | 32442 | nd | nd | 0.03 | C | Narrow |
| Bossert (52) | 2006 | Pulmonary artery rupture | Surgical ICU | 2860 | nd | nd | 0.07 | C | Narrow |
| *Total* | | *Pulmonary artery rupture* | | *35302* | | | *0.03%* [a] | | |
| Shah (57) | 1984 | Pulmonary hemorrhage | nd | 6245 | 62 | nd | 0.06 | C | Moderate |
| Sandham (37) | 2003 | Pulmonary hemorrhage | Surgical ICU | 941 (965) | 72 | 70 | 0.3 (0) NS | A | Moderate |
| Boyd (53) | 1983 | Pulmonary hemorrhage | All | 500 | nd | nd | 0.2 | B | Narrow |
| ESCAPE (14) investigators | 2005 | Pulmonary infarction / hemorrhage | Cardiac ICU | 215 | 56 | 74 | 0.9 | A | Moderate |
| *Total* | | *Pulmonary hemorrhage* | | *7901* | | | *0.1%* [a] | | |

ICU, intensive care unit; OR, operating room; nd, no data; PAC, pulmonary artery catheter.

[a] Simple pooled (averaged) estimate. I.e., weighted only by sample size. All summary percentages are likely to be overestimates since studies without events that did not explicitly report no events are not included.

**Table 14. Incidence of clinically significant infections related complications in patients with PAC (or control, in parentheses). See Table 7 for data from RCTs on other, non-PAC-attributed infections.**

| Author | Year | Adverse Event | Setting | No. Analyzed | Mean Age (yr) | Male (%) | % with Adverse Event | Quality | Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Boyd (53) | 1983 | Endocarditis | All | 500 | nd | nd | 0 | B | Narrow |
| ESCAPE (14) investigators | 2005 | "PAC-related infection" | Cardiac ICU | 215 | 56 | 74 | 1.9 | A | Moderate |
| Wheeler (15) | 2006 | Septicemia & other infections [a] | ICU | 513 | 49 | 45 | 1.0 | A | Narrow |
| Sandham (37) | 2003 | Sepsis | Surgical ICU | 941 (965) | 72 | 70 | 1.3 (1.3) NS | A | Moderate |
| Wheeler (15) | 2006 | Septicemia | ICU | 513 | 49 | 45 | 1.0 | A | Narrow |
| Boyd (53) | 1983 | Septicemia | All | 500 | nd | nd | 1.3 | B | Narrow |
| Richard (36) | 2003 | Septicemia | ICU (mixed units) | 342 | 62 | 67 | 3 | B | Moderate |
| Valentine (7) | 1998 | Sepsis | Surgical ICU | 60 | 64 | 100 | 3 | B | Narrow |
| *Total* | | *Sepsis* | | *2356* | | | *1.6%* [b] | | |

ICU, intensive care unit; nd, no data; PAC, pulmonary artery catheter.

[a] Not including "local" infections

[b] Simple pooled (averaged) estimate. I.e., weighted only by sample size. All summary percentages are likely to be overestimates since studies without events that did not explicitly report no events are not included.

**Table 15. Incidence of embolism related events in patients with PAC (or control, in parentheses). See Table 6 for data from RCTs on other, non-PAC-attributed pulmonary outcomes.**

| Author | Year | Adverse Event | Setting | No. Analyzed | Mean Age (yr) | Male (%) | % with Adverse Event | Quality | Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Wheeler (15) | 2006 | Air embolism | ICU | 513 | 49 | 45 | 0.6 | A | Narrow |
| Sandham (37) | 2003 | Pulmonary embolism | Surgical ICU | 941 (965) | 72 | 70 | 0.9 (0) P=.004 | A | Moderate |
| Wheeler (15) | 2006 | Pulmonary embolism or deep vein thrombosis | ICU | 513 | 49 | 45 | 0 | A | Narrow |
| Boyd (53) | 1983 | Pulmonary embolism | All | 500 | nd | nd | 0.4 | B | Narrow |
| Richard (36) | 2003 | Pulmonary embolism | ICU (mixed units) | 342 | 62 | 67 | 0 | B | Moderate |
| *Total* | | *Pulmonary embolism* | | *2296* | | | *0.5%* [a] | | |
| Sandham (37) | 2003 | Pulmonary infarction | Surgical ICU | 941 (965) | 72 | 70 | 0.1 (0) NS | A | Moderate |

ICU, intensive care unit; nd, no data; PAC, pulmonary artery catheter.

[a] Simple pooled (averaged) estimate. I.e., weighted only by sample size. All summary percentages are likely to be overestimates since studies without events that did not explicitly report no events are not included.

**Table 16. Incidence of catheter knotting at PAC removal**

| Author | Year | Adverse Event | Setting | No. Analyzed | Mean Age (yr) | Male (%) | % with Adverse Event | Quality | Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Bossert (52) | 2006 | Catheter knotting | Surgical ICU | 2860 | nd | nd | 0.03 | C | Narrow |
| Richard (36) | 2003 | Catheter knotting | ICU (mixed units) | 342 | 62 | 67 | 1.8 | B | Moderate |
| ESCAPE (14) investigators | 2005 | Catheter knotting | Cardiac ICU | 215 | 46 | 74 | 0.9 | A | Moderate |
| *Total* | | *Catheter knotting* | | *3417* | | | *0.3%* [a] | | |

ICU, intensive care unit; nd, no data; PAC, pulmonary artery catheter.

[a] Simple pooled (averaged) estimate. I.e., weighted only by sample size. All summary percentages are likely to be overestimates since studies without events that did not explicitly report no events are not included.

**Table 17. Incidence of death directly connected with PAC**

| Author | Year | Adverse Event | Setting | No. Analyzed | Mean Age (yr) | Male (%) | % with Adverse Event | Quality | Applicability |
|---|---|---|---|---|---|---|---|---|---|
| Shah (57) | 1984 | Death (uncontrolled hemorrhage) | nd | 6245 | 62 | nd | 0.02 | C | Moderate |
| Wheeler (15) | 2006 | Death (due to PAC) | ICU | 513 | 49 | 45 | 0 | A | Narrow |
| Boyd (53) | 1983 | Death (due to PAC) | All | 500 | nd | nd | 0 | B | Narrow |
| ESCAPE (14) investigators | 2005 | Death (related to PAC) | Cardiac ICU | 215 | 56 | 74 | 0 | A | Moderate |
| Shoemaker (39) | 1988 | Death (or other major event) | Surgical ICU | 174 | 54 | 62 | 0 | B | Narrow |
| Bender (5) | 1997 | Death (or other major event) | Surgical ICU | 51 | 65 | 63 | 0 | B | Narrow |
| Bonazzi (30) | 2002 | Death (or other major event) | Surgical ICU | 50 | 67 | 100 | 0 | B | Narrow |
| Joyce (40) | 1990 | Death (or other major event) | Surgical ICU | 21 | 68 | 68 | 0 | B | Narrow |
| *Total* | | *Death* | | *7769* | | | *0.01%* [a] | | |

ICU, intensive care unit; nd, no data; PAC, pulmonary artery catheter.

[a] Simple pooled (averaged) estimate. I.e., weighted only by sample size. All summary percentages are likely to be overestimates since studies without events that did not explicitly report no events are not included.

# Chapter 4. Discussion

As described in the introduction and in the narrative reviews in response to questions 1 and 2 (describing the available technologies to assess cardiac output and manage volume status, and describing the specific indications for pulmonary artery catheter [PAC] use), PAC is an important tool for management of select patients in intensive care settings. However, since its introduction, PAC use has propagated to a wide range of patients in multiple settings. By helping to quantify, and thus to manage cardiac output and volume status, PAC is commonly used to guide therapy and is seen as beneficial to the patients and clinicians. However, the benefits of the routine use of PAC for broad groups of patients have not been substantiated by randomized controlled trials (RCTs) in the setting of risks of adverse events due to this invasive intervention.

Overall, the evidence suggests no benefit of the routine use of PAC in the ICU to large groups of patients within trials. The evidence also documents a wide range of risks of PAC use; though adverse events are relatively rare and serious adverse events are very rare. Since 1985, 16 randomized trials have compared routine PAC use to either no PAC or to central venous pressure (CVP) monitoring. With the exception of the first reported trial (38), the trials consistently found no difference in mortality or length of stay (LOS) in the intensive care unit (ICU) or hospital. The summary odds ratio (OR) of death was 1.03 (95% confidence interval [CI] 0.9, 1.2), the difference in hospital LOS was +0.3 (95% CI, -0.4, 1.0; favoring no PAC) days, and the difference in ICU LOS was 0 (95% CI –0.5, 0.5) days.

The studies were clinically heterogeneous. In addition to the two different types of controls (no invasive monitoring and CVP monitoring), studies were performed in a range of ICU settings, in patients with a wide range of both medical and surgical morbidities, across various countries, over a long time period during which the standards of ICU care have changed considerably, and in patients with different underlying risks of clinical events. Despite the large degree of clinical heterogeneity among the studies the studies were statistically homogenous in their results – almost all found no clinically or statistically significant differences. This consistency of results in the setting of diverse studies adds credibility to the conclusion that in trials, patient outcomes are similar regardless of use of PAC. The average age of patients in studies was generally over 60 years. It is likely that nearly half the patients across studies would be Medicare-eligible, based on age. Thus, the patients included in studies of PAC are fairly-well applicable to the Medicare population. However, it is possible that differences in the benefit of PAC are hidden within the studies. No study evaluated the how the effect of PAC varied with patient age and no conclusions could be drawn from comparison across studies based on average patient age.

Importantly, most trials generally either explicitly or implicitly excluded patients for whom the treating physician determined that PAC was absolutely necessary. However, the studies used a broad range of eligibility criteria, making it difficult to assess exactly how applicable the individual trials and the totality of the studies are for a given group of patients. All; but two of the 16 trials reported excluding patients who were at “high risk” – variously defined as requiring inotropic drugs, having severe medical conditions, or unstable – or for whom PAC was an ethical imperative, mandatory, indicated, or there was lack of physician equipoise regarding PAC use. Among trials that reported how many patients were excluded for stated reasons, between 0.5 and 52 percent of patients were thus excluded (with a median of 2 percent). Only one trial of about 200 patients explicitly limited the studied participants to those

considered to "requir[e] a PAC," though one patients was still excluded for ethical reasons.(34) Only one trial (of patients at high risk of dying after surgery) apparently did not exclude patients with "too high" a risk without PAC.[Shoemaker 88 90], but instead excluded patients who were not sufficiently ill to require intensive monitoring. Overall, then, the findings of these trials can be applied only to patients who would be enrolled in a trial on the basis of their not requiring PAC for some reason. For the most part, the studies evaluated the routine use of PAC in patients who were deemed to not necessarily need PAC, instead of attempting to determine whether PAC may be of value for particular patients for whom it can be hypothesized that the intervention would be of particular value. It remains unknown how much, if at all, the sickest, potentially highest risk patients benefit from PAC compared to noninvasive monitoring. Because of this the evidence provides only an incomplete answer to the question (Key Question 3) of whether therapeutic management of cardiac output and volume status based on pulmonary artery catheter monitoring in critical care settings leads to improved patient outcomes compared to noninvasive and less invasive techniques.

A potential threat to the validity of these studies is crossover of interventions. Only 9 of 16 studies reported rates of crossover (patients assigned to control, but received PAC); of these the crossover rates were relatively low (less than 10 percent) in most, but very high (47 and 64 percent) in two small studies. While it is possible that crossover of patients dampened any effects of PAC (by making it more likely that event rates were similar in the two arms) the low crossover rates in the larger studies limits the overall effect of crossover on the summary results and thus the conclusions.

Most of the trials also reported some data on relative rates of various medical morbidities; primarily cardiovascular, pulmonary, and renal events. These morbidities related to the underlying disease states of the patients (i.e., the reasons that they required ICU management), not specifically due to adverse events due to invasive monitoring. The findings across studies were highly inconsistent with several studies finding no differences in event rates and the remaining studies equally distributed among those that found higher event rates in those with PAC monitoring and those with higher rates in the control arms. There was no easily discernable pattern based on underlying medical or surgical condition, setting, time period (year), specific medical morbidity, or other factors. Overall across studies, about the same rate of medical morbidities were reported among patients with PAC as without PAC.

Only three trials reported on duration of ventilation. All found no statistically significant difference between PAC and no PAC, although one study found that patients with PAC had a much greater duration of ventilation than those without PAC (35 vs. 6 hours). The four studies that evaluated quality of life (or disease severity) had differing findings. A large well-conducted trial found greater improvement in the Minnesota Living with Heart Failure questionnaire at 1 month, but not 6 months, with PAC; but no differences in other measures of patient symptoms. In contrast, a small trial found that APACHE scores were statistically significantly worse after PAC use than without PAC at discharge from the intensive care unit; however, the APACHE score was not designed, nor has it been validated, for longitudinal testing. Two studies that used the Systemic Organ Failure Assessment (SOFA) score found no difference between interventions.

The use of PAC provides only diagnostic information, which if used appropriately can help to guide therapeutic management of shock and other conditions requiring hemodynamic monitoring. The efficacy of the test to provide an intervention to improve outcome is based on the accuracy of interpretation as well as whether the information is acted upon appropriately. The

questions of interest pertain to the clinical benefit of using PAC in intensive care settings, as opposed to accuracy of diagnosis. In Fryback's and Thornbury's model, the evidence considered here are at Level 5, evaluating "patient outcome efficacy, " how using the diagnostic tool impacts on clinical benefits (20). It is possible that the lack of benefit from PAC use among these studies is related to ineffective or improper changes in management strategy based on PAC data rather than to a lack of potential benefit of the PAC data. None of the studies used a specific protocol for use of the PAC data, though Wheeler 2006 (15) did set targets for fluid and circulation maintenance based in part on PAC or CVP data. Three studies (including the Wheeler study) did report significantly greater use of fluids, vasoactive drugs, and/or diuretics, but even these found no clinical benefits overall. Nevertheless, it is reasonable to contend that improvements in effective management strategies for critically ill patients may result in clinical benefits from PAC placement in the future. However, currently, given the ways that PAC data are acted upon, as evidenced from the published trials, the value of PAC in broadly defined populations of intensive care patients is unproven.

Given the lack of evidence of benefit for the routine use of PAC across large groups of patients, the adverse events related to PAC play a particularly important role in its evaluation. As listed in Table 10, a large number of clinically important, and sometimes disastrous, adverse events are known to occur due to the risks involved in inserting, maintaining, and removing a PAC. While some of the adverse events may often be relatively easy to treat or are self-limited (e.g., arrhythmias, hemorrhage, infection), many of the adverse events are life-threatening or require emergency surgery or interventional radiology procedures. Clinically significant arrhythmias, carotid artery punctures, clinically important septicemia, pneumothorax, hemothorax, and pulmonary embolism each occurred in studies between about 0.5 and 3 percent of patients. An important caveat, though, is that the data on the relative rates between PAC placement and CVP placement or noninvasive monitoring of complications (or adverse events) that might be attributed to central line placement have not been adequately reported. Few comparative studies reported event rates for both arms and no trial clearly reported events attributed to CVP placement. Thus it is in fact difficult to judge the balance between lack of benefit of PAC in populations of patients (where benefits to individual patients may thus be rare) with rare complications in individual patients.

Among the trials and large cohort studies reviewed, only one death "due to PAC" was reported among up to almost 17,000 patients (depending on whether one counts studies that did not mention PAC-related deaths). However, the manufacturer and user facility device experience database gathered by the Food and Drug Administration (FDA) has reports of 48 deaths associated with PAC between 1993 and 1999 (48). Of course, these analyses only evaluate those deaths that were determined to caused by PAC, correctly or not, and does not include other deaths that may have in fact ultimately have been due to PAC placement.

Future research is needed to determine which patients, if any, in what settings and circumstances, may benefit. In general the studies so far have excluded patients for whom the treating physician felt that it was not ethically appropriate to withhold PAC. Patients who are in cardiogenic shock or on inotropic therapy have generally been excluded. Other patients who may potentially benefit from the placement of PAC are those with advanced heart failure for whom a clinical assessment of volume status is not possible (e.g., obese patients), patients in whom there is a discrepancy in clinical assessment and patient symptomatology, and patients with hypotension and pulmonary congestion. However, RCTs may not be possible in these patient populations as treating physicians would not be willing to randomize them. Nevertheless, as best

as possible, given the limitations on who can be enrolled, future RCTs should focus on specific populations of patients who might benefit from PAC, as opposed to additional trials of patients for whom PAC use is only reasonable or of possible value. At this point, observational studies may be the only practical way to answer the question of whether the patients who are believed to need PAC really do benefit from the intervention. However, any such study would need to be excellent quality and use rigorous methods to adjust for confounding differences among those patients who receive PAC or not. Preferably, such studies should use multiple methods for adjusting for confounders and baseline risks, performing sensitivity analyses, to strengthen their conclusions. Any future studies should continue to focus primarily on clinical benefits and harms as short-term intermediate outcomes are inadequate surrogates for clinically important outcomes. The methods section of the ESCAPE trial (14) states that "a concurrent PAC registry was established to characterize hospitalized patients receiving PACs considered to be required during heart failure management." It is hoped that this registry will provide more insight into this population; however, unless the registry is including patients who are thought to require PAC, but do not in fact receive it, and the analysis successfully accounts for baseline differences between these patients and those receiving PAC, it is likely that the ESCAPE registry will only incompletely assess the relative value of PAC use in this population. Only two studies have reported on subgroup analyses. Both found that there were no statistically significant differences in mortality with or without PAC, regardless of subgroup; however, neither study had enrolled enough patients for these analyses to rule out true differences across subgroups. Patient level metaanalysis of these two studies and other large trials may be helpful in finding any groups of patients who are more likely to benefit from PAC use. In this type of analysis, the patient-level data from all included studies are combined allowing more refined analyses than are possible from study-level metaanalyses of reported data.

As the only proven way to assess hemodynamic data, it is important that we do not abolish PAC completely but use it judiciously. It is important for any new trials looking at hemodynamic data (to assess newer therapies or for other technology to assess hemodynamics) to consider a central core lab to evaluate the accuracy of readings as well as provide treatment algorithms to standardize intervention based on the hemodynamic data. The available evidence does not consider many special circumstances where there may be reason to suppose that PAC is of value. However, the evidence does support the conclusion that in patients for whom PAC use is not deemed absolutely necessary, the routine use of PAC does not improve long-term clinical outcomes. At the same time, PAC use imposes uncommon, but identifiable, risks of adverse events. Physicians should be educated about the risks and benefits of PAC-directed therapy to allow for judicious decisions about its use on an individual basis.

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# Appendix A. MEDLINE search strategy

## MEDLINE 1966-September Week 2 2006

| # | History | Search Results |
|---|---|---|
| 1 | (artery adj2 catheter$).tw. | 3994 |
| 2 | pulmonary.mp. | 348197 |
| 3 | 1 and 2 | 2557 |
| 4 | exp Catheterization, Swan-Ganz/ | 1620 |
| 5 | exp Thermodilution/ | 1841 |
| 6 | S-G catheter.mp. | 2 |
| 7 | Swan-Ganz.mp. | 3092 |
| 8 | or/3-7 | 6338 |
| 9 | limit 8 to humans | 5494 |
| 10 | limit 9 to "all adult (19 plus years)" | 3527 |
| 11 | 9 not 10 | 1967 |
| 12 | limit 11 to "all child (0 to 18 years)" | 195 |
| 13 | 9 not 12 | 5299 |
| 14 | limit 13 to english language | 4323 |
| 15 | limit 14 to (guideline or meta analysis or practice guideline or "review") | 359 |
| 16 | 14 not 15 | 3964 |
| 17 | follow-up studies/ | 339797 |
| 18 | (follow-up or followup).tw. | 347111 |
| 19 | exp Case-Control Studies/ | 339945 |
| 20 | (case adj20 control).tw. | 46309 |
| 21 | exp Longitudinal Studies/ | 563121 |
| 22 | longitudinal.tw. | 69039 |
| 23 | (random$ or rct).tw. | 369848 |
| 24 | exp Randomized Controlled Trials/ | 48201 |
| 25 | exp random allocation/ | 58870 |
| 26 | exp Double-Blind Method/ | 91075 |
| 27 | exp Single-Blind Method/ | 10636 |
| 28 | randomized controlled trial.pt. | 234619 |
| 29 | clinical trial.pt. | 457763 |
| 30 | multicenter study.pt. | 83156 |
| 31 | controlled clinical trials/ | 3400 |
| 32 | (clin$ adj trial$).tw. | 106615 |
| 33 | ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. | 87186 |
| 34 | exp PLACEBOS/ | 25749 |
| 35 | placebo$.tw. | 100882 |
| 36 | exp Cohort Studies/ | 609650 |
| 37 | cohort.tw. | 87211 |
| 38 | exp Research Design/ | 217545 |

| | | |
|---|---|---|
| 39 | exp Evaluation Studies/ | 597331 |
| 40 | exp Prospective Studies/ | 219773 |
| 41 | exp Comparative Study/ | 1349008 |
| 42 | or/17-39 | 3050006 |
| 43 | 16 and 42 | 1918 |
| 44 | limit 43 to comment and (letter or editorial).pt. | 61 |
| 45 | limit 43 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or news or newspaper article or patient education handout or periodical index) | 67 |
| 46 | 43 not (44 or 45) | 1811 |

# Appendix B. Data extraction form

| Author | | Year | | Ref ID | | UI | | Reviewer | |
|---|---|---|---|---|---|---|---|---|---|
| Study Design (from perspective of PAC) | | Country | | Multicenter? (Y/N) | | Calendar Years of study | | Funding Source | |
| | | | | | | | | | |

| | | | |
|---|---|---|---|
| Type (Description) of PAC used | | | |
| Who inserted PAC? | | | |
| Comparator (Description) | | | |
| Inclusion Criteria | | Exclusion Criteria | |
| Other Population Description | | Setting* | |
| Comments | | | |

| CHARACTERISTICS | | PAC | Control |
|---|---|---|---|
| No. Enrolled | | | |
| Mean Age | | | |
| Age Range | metric | | |
| % Male | | | |
| Baseline Severity Measure**: | | | |
| Range | metric: | | |
| Baseline Severity Measure: | | | |
| Range | metric: | | |
| Duration of PAC Exposure | | | |
| Duration of Patient Followup | | | |
| Comments: | | | |

* e.g., medical ICU, cardiac ICU, surgical ICU, Intra-op, Post-op, other
**e.g., APACHE score, etc

**QUALITY ISSUES**

| Method of randomization | Adequate allocation concealment (Y/N/nd) | Intention to treat? (Y/N) | Outcome assessors blinded? (Y/N) | Loss to followup (%) | Were the results adjusted? (Y/N) | Were groups similar at baseline? (Y/N) | Recruitment method appropriate*? (Y/N) |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| List the variables that were adjusted for: | | | | | | | |
| Comments | | | | | | | |

*Appropriate consecutive or randomized

RESULTS: Events etc.

| Outcome | Definition | PAC | | Control | | Unadjusted | | | Adjusted | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No. Analyzed | No. Events | No. Analyzed | No. Events | OR/RR** | 95% CI** | P between | OR/RR** | 95% CI** | P between |
| **Mortality** | | | | | | | | | | | |
| **Length of ICU stay** | | | | | | | | | | | |
| **Length of hospital stay** | | | | | | | | | | | |
| **Duration of Ventilation** | | | | | | | | | | | |
| **Medical Complications*** | | | | | | | | | | | |
| **Other**** | | | | | | | | | | | |
| **Other**** | | | | | | | | | | | |
| **Other**** | | | | | | | | | | | |
| **AE: Bleeding** | | | | | | | | | | | |
| **AE: Arrhythmia** | | | | | | | | | | | |
| **AE: Infection** | | | | | | | | | | | |
| **AE: Insertion complication** | | | | | | | | | | | |
| **AE: Pneumothorax** | | | | | | | | | | | |
| **AE: Other**** | | | | | | | | | | | |
| **AE: Other**** | | | | | | | | | | | |
| **AE: Other**** | | | | | | | | | | | |

* Eg, cardiac or pulmonary complications, not directly related to PAC, not AE

** Replace “Other**” with actual Outcome and “OR/RR**” with actual metric and “95% CI**” with SE, if necessary

**RESULTS: Continuous measures**

| Outcome | Definition (units) | Group | No. Analyzed | Baseline | Final | Change | P Within | Net Change | P between |
|---|---|---|---|---|---|---|---|---|---|
| **Symptoms** | | **PAC** | | | | | | | |
| | | **Control** | | | | | | | |
| **Optimization of treatment** | | **PAC** | | | | | | | |
| | | **Control** | | | | | | | |
| **Other**** | | **PAC** | | | | | | | |
| | | **Control** | | | | | | | |
| **Other**** | | **PAC** | | | | | | | |
| | | **Control** | | | | | | | |

| **APPLICABILITY** | | **QUALITY** | |
|---|---|---|---|
| | **Wide Applicability**: sample representative of Medicare population in relevant setting. Patient's age (older adult), gender, spectrum of disease severity and type, etc are representative of population of interest.<br>PACs used within past 10 years (1997-2006). | | **A Good quality**: Prospective, no obvious biases or reporting errors, <20% dropout, complete reporting of data.<br>If comparative study: Must be RCT.<br>If study on adverse events: Must be prospective. |
| | **Moderate Applicability**: sample is an important sub-group of population of interest. Possibly limited to a narrow or young age range, type of disease, gender etc.<br>PACs used within past 20 years (1987-2006). | | **B Fair quality**: Problems with study/paper unlikely to cause major bias.<br>If comparative study: Must be RCT.<br>If study on adverse events: Must be prospective. |
| | **Narrow Applicability**: sample represents only a narrow, atypical subgroup of population of interest, or old study. | | **C Poor quality**: Prospective or retrospective. Cannot exclude possible significant biases. Poor methods, incomplete data, reporting errors.<br>All non-RCT comparative studies graded C<br>All retrospective studies of AE graded C |
| **If applicability is graded narrow or moderate, what are the limiting factors?** | | **If Quality is rated B or C, what are the limiting factors? (i.e., incomplete data, errors in analysis, definitions not clear, poor follow-up, dropouts)** | |
| | | | |

**SUMMARY TABLE TEMPLATES**

**Comparative Studies (PAC vs Control), All outcomes, including AE**

Study Design

| Outcome | Study, Year | Setting | No. Analyzed (Enrolled) | | Control Used | Mean Age* (yr) | % Male* | Baseline or Event Rate* | Results | | | | Quality | Applicability to Setting |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | PAC | Control | | | | | Metric/ Units | PAC | Control | P Between | | |

* PAC group

**"Cohort" Studies (PAC only), only AE**

| Adverse Event | Study, Year | Setting | No. Analyzed (Enrolled) | Mean Age (yr) | % Male | % with Adverse Event | Quality | Applicability to Setting |
|---|---|---|---|---|---|---|---|---|

* PAC group

# Appendix C. Articles evaluated

| Author | Title | Date | UI/PMID | Journal | Topic |
|---|---|---|---|---|---|
| Bender JS | Routine pulmonary artery catheterization does not reduce morbidity and mortality of elective vascular surgery: results of a prospective, randomized trial | 1997 | 9339929 | Annals of Surgery | Clinical outcome |
| Berlauk JF | Preoperative optimization of cardiovascular hemodynamics improves outcome in peripheral vascular surgery. A prospective, randomized clinical trial | 1991 | 1929610 | Annals of Surgery | Clinical outcome |
| Binanay C, ESCAPE | Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial | 2005 | 16204662 | JAMA | Clinical outcome |
| Bonazzi M | Impact of perioperative haemodynamic monitoring on cardiac morbidity after major vascular surgery in low risk patients. A randomised pilot trial | 2002 | 12027474 | European Journal of Vascular & Endovascular Surgery | Clinical outcome |
| Guyatt G | A randomized control trial of right-heart catheterization in critically ill patients. Ontario Intensive Care Study Group | 1991 | 10147952 | Journal of Intensive Care Medicine | Clinical outcome |
| Harvey S | Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial | 2005 | 16084255 | Lancet | Clinical outcome |
| Isaacson IJ | The value of pulmonary artery and central venous monitoring in patients undergoing abdominal aortic reconstructive surgery: a comparative study of two selected, randomized groups | 1990 | 2243411 | Journal of Vascular Surgery | Clinical outcome |
| Joyce WP | The role of central haemodynamic monitoring in abdominal aortic surgery. A prospective randomised study | 1990 | 2279574 | European Journal of Vascular Surgery | Clinical outcome |
| Pearson KS | A cost/benefit analysis of randomized invasive monitoring for patients undergoing cardiac surgery. | 1989 | 2505641 | Anesthesia & Analgesia | Clinical outcome |
| Rhodes A | A randomised, controlled trial of the pulmonary artery catheter in critically ill patients | 2002 | 11904653 | Intensive Care Medicine | Clinical outcome |
| Richard C | Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: a randomized controlled trial | 2003 | 14645314 | JAMA | Clinical outcome |
| Sandham JD | A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients | 2003 | 12510037 | New England Journal of Medicine | Clinical outcome |
| Schultz RJ | The role of physiologic monitoring in patients with fractures of the hip | 1985 | 3989888 | Journal of Trauma-Injury Infection & Critical Care | Clinical outcome |
| Shoemaker WC | Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients | 1988 | 3191758 | Chest | Clinical outcome |

| Author | Title | Date | UI/PMID | Journal | Topic |
|---|---|---|---|---|---|
| Shoemaker WC | The efficacy of central venous and pulmonary artery catheters and therapy based upon them in reducing mortality and morbidity | 1337 | 2222172 | Archives of Surgery | Clinical outcome |
| Valentine RJ | Effectiveness of pulmonary artery catheters in aortic surgery: a randomized trial | 1998 | 9510275 | Journal of Vascular Surgery | Clinical outcome |
| Wheeler AP | Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury | 2006 | 16714768 | New England Journal of Medicine | Clinical outcome |
| Bossert T | Swan-Ganz catheter-induced severe complications in cardiac surgery: right ventricular perforation, knotting, and rupture of a pulmonary artery | 2006 | 16684066 | Journal of Cardiac Surgery | Adverse events |
| Boyd KD | A prospective study of complications of pulmonary artery catheterizations in 500 consecutive patients | 1983 | 6884097 | Chest | Adverse events |
| Cohen MG | Pulmonary artery catheterization in acute coronary syndromes: insights from the GUSTO IIb and GUSTO III trials | 2005 | 15866250 | American Journal of Medicine | Adverse events |
| Damen J | A prospective analysis of 1,400 pulmonary artery catheterizations in patients undergoing cardiac surgery | 1986 | 3766094 | Acta Anaesthesiologica Scandinavica | Adverse events |
| Kearney TJ | Pulmonary artery rupture associated with the Swan-Ganz catheter | 1995 | 7587440 | Chest | Adverse events |
| Lopez-Sendon J | Right ventricular infarction as a risk factor for ventricular fibrillation during pulmonary artery catheterization using Swan-Ganz catheters | 1990 | 2296867 | American Heart Journal | Adverse events |
| Shah KB | A review of pulmonary artery catheterization in 6,245 patients | 1984 | 6476435 | Anesthesiology | Adverse events |
| Webster CS | A prospective clinical audit of central venous catheter use and complications in 1000 consecutive patients | 2003 | 12635401 | Anaesthesia & Intensive Care | Adverse events |

# Appendix D. Rejected Articles

Anonymous. The SvO2 study: general design and results of the feasibility phase of a multicenter, randomized trial of three different hemodynamic approaches and two monitoring techniques in the treatment of critically ill patients. The SvO2 Collaborative Group. Controlled Clinical Trials. 1995. (UI 7743791).
**Report of study design**

Adams JG, Clifford EJ, Henry RS, Poulos E. Selective monitoring in abdominal aortic surgery. American Surgeon. 1993. (UI 8368660).
**AE, N<500**

Afessa B, Spencer S, Khan W, LaGatta M, Bridges L, Freire AX. Association of pulmonary artery catheter use with in-hospital mortality. Critical Care Medicine. 2001. (UI 11395590).
**No AE data**

Aikawa N, Sumiyama Y, Kusachi S, Hirasawa H, Oda S, Yamazaki Y. Use of antifungal agents in febrile patients nonresponsive to antibacterial treatment: the current status in surgical and critical care patients in Japan. Journal of Infection & Chemotherapy. 2002. (UI 12373487).
**AE, N<500**

Aitken LM. Reliability of measurements of pulmonary artery pressure obtained with patients in the 60 degrees lateral position.. American Journal of Critical Care. 2000. (UI 10631390).
**AE, N<500**

Albert NM, Spear BT, Hammel J. Agreement and clinical utility of 2 techniques for measuring cardiac output in patients with low cardiac output. American Journal of Critical Care. 1999. (UI 9987544).
**AE, N<500**

Amshel CE, Palesty JA, Dudrick SJ. Are chest X-rays mandatory following central venous recatheterization over a wire?. American Surgeon. 1998. (UI 9619168).
**Not PAC**

Bach A, Bohrer H, Geiss HK. Safety of a guidewire technique for replacement of pulmonary artery catheters. Journal of Cardiothoracic & Vascular Anesthesia. 1992. (UI 1472669).
**AE, N<500**

Bach A, Stubbig K, Geiss HK. Infectious risk of replacing venous catheters by the guide-wire technique. Zentralblatt fur Hygiene und Umweltmedizin. 1992. (UI 1388616).
**AE, N<500**

Bernard GR, Luce JM, Sprung CL, Rinaldo JE, Tate RM, Sibbald WJ, Kariman K, Higgins S, Bradley R, Metz CA. High-dose corticosteroids in patients with the adult respiratory distress syndrome. New England Journal of Medicine. 1987. (UI 3317054).
**AE, N<500**

Berthelsen PG, Eldrup N, Nilsson LB, Rasmussen JP. Thermodilution cardiac output. Cold vs room temperature injectate and the importance of measuring the injectate temperature in the right atrium. Acta Anaesthesiologica Scandinavica. 2002. (UI 12366505).
**AE, N<500**

Bilen Z, Weinberg PF, Gowani Y, Cohen IL, Socaris S, Fein IA. Clinical utility and cost-effectiveness of protective sleeve pulmonary artery catheters. Critical Care Medicine. 1991. (UI 1902154).
**AE, N<500**

Bishop MH, Shoemaker WC, Appel PL, Meade P, Ordog GJ, Wasserberger J, Wo CJ, Rimle DA, Kram HB, Umali R. Prospective, randomized trial of survivor values of cardiac index, oxygen delivery, and oxygen consumption as resuscitation endpoints in severe trauma.. Journal of Trauma-Injury Infection & Critical Care. 1995. (UI 7760409).
**AE, N<500**

Catheter-induced pulmonary arterial trauma: can it always be averted?. Stone JG, Khambatta HJ, McDaniel DD. Journal of Thoracic & Cardiovascular Surgery. 1983. (UI 6602913).
**AE, N<500**

Celoria G, Steingrub JS, Vickers-Lahti M, Teres D, Stein KL, Fink M, Friedmann P. Clinical assessment of hemodynamic values in two surgical intensive care units. Effects on therapy. Archives of Surgery. 1990. (UI 2378556).
**AE, N<500**

Chang MC, Black CS, Meredith JW. Volumetric assessment of preload in trauma patients: addressing the problem of mathematical coupling.. Shock. 1996. (UI 8946646).
**AE, N<500**

Chang MC, Meredith JW, Kincaid EH, Miller PR. Maintaining survivors' values of left ventricular power output during shock resuscitation: a prospective pilot study. Journal of Trauma-Injury Infection & Critical Care. 2000. (UI 10912854).
**AE, N<500**

Chang MC, Mondy JS, Meredith JW, Holcroft JW. Redefining cardiovascular performance during resuscitation: ventricular stroke work, power, and the pressure-volume diagram. Journal of Trauma-Injury Infection & Critical Care. 1998. (UI 9751535).
**AE, N<500**

Chawla LS, Zia H, Gutierrez G, Katz NM, Seneff MG, Shah M. Lack of equivalence between central and mixed venous oxygen saturation.. Chest. 2004. (UI 15596689).
**AE, N<500**

Chen YY, Yen DH, Yang YG, Liu CY, Wang FD, Chou P. Comparison between replacement at 4 days and 7 days of the infection rate for pulmonary artery catheters in an intensive care unit.. Critical Care Medicine. 2003. (UI 12771602).
**AE, N<500**

Chittock DR, Dhingra VK, Ronco JJ, Russell JA, Forrest DM, Tweeddale M, Fenwick JC. Severity of illness and risk of death associated with pulmonary artery catheter use.. Critical Care Medicine. 2004. (UI 15071376).
**No AE data**

Christoforidis D, Chassot PG, Mosimann F, Lienard D, Brunstein F, Bejko D, Lejeune FJ, Chiolero R. Isolated limb perfusion: distinct tourniquet and tumor necrosis factor effects on the early hemodynamic response. Archives of Surgery. 2003. (UI 12511144).
**AE, N<500**

Cieslinski G, Konrad T, Klepzig H. Comparison of calculated and measured mixed venous oxygen saturation in critically ill patients. Infusionstherapie und Transfusionsmedizin. 1995. (UI 8589593).
**AE, N<500**

Cobb DK, High KP, Sawyer RG, Sable CA, Adams RB, Lindley DA, Pruett TL, Schwenzer KJ, Farr BM. A controlled trial of scheduled replacement of central venous and pulmonary-artery catheters.. New England Journal of Medicine. 1992. (UI 1522842).
**AE, N<500**

Cohen Y, Fosse JP, Karoubi P, Reboul-Marty J, Dreyfuss D, Hoang P, Cupa M. The 'hands-off' catheter and the prevention of systemic infections associated with pulmonary artery catheter: a prospective study. American Journal of Respiratory & Critical Care Medicine. 1998. (UI 9445311).
**AE, N<500**

Coles NA, Hibberd M, Russell M, Love T, Ory D, Field TS, Dec GW, Eagle KA. Potential impact of pulmonary artery catheter placement on short-term management decisions in the medical intensive care unit.. American Heart Journal. 1993. (UI 8213436).
**AE, N<500**

Connors AF, Speroff T, Dawson NV, Thomas C, Harrell FE, Wagner D, Desbiens N, Goldman L, Wu AW, Califf RM, Fulkerson WJ, Vidaillet H, Broste S, Bellamy P, Lynn J, Knaus WA. The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators.. JAMA. 1996. (UI 8782638).
**No AE data**

Cotter G, Moshkovitz Y, Kaluski E, Milo O, Nobikov Y, Schneeweiss A, Krakover R, Vered Z. The role of cardiac power and systemic vascular resistance in the pathophysiology and diagnosis of patients with acute congestive heart failure.. European Journal of Heart Failure. 2003. (UI 12921805).
**AE, N<500**

Damen J. Ventricular arrhythmias during insertion and removal of pulmonary artery catheters. Chest. 1985. (UI 4017671).
**AE, N<500**

Damen J. Infectious complications of simultaneously inserted central venous and pulmonary artery catheters. Netherlands Journal of Surgery. 1987. (UI 3683940).
**No AE data**

Decailliot F, Cherqui D, Leroux B, Lanteri-Minet M, Ben SS, Husson E, Duvaldestin P, Stephan F. Effects of portal triad clamping on haemodynamic conditions during laparoscopic liver resection. British Journal of Anaesthesia. 2001. (UI 11517137).
**AE, N<500**

Del Guercio LR, Savino JA, Morgan JC. Physiologic assessment of surgical diagnosis-related groups. Annals of Surgery. 1985. (UI 3931595).
**AE, N<500**

Della RG, Costa MG, Coccia C, Pompei L, Pietropaoli P. Preload and haemodynamic assessment during liver transplantation: a comparison between the pulmonary artery catheter and transpulmonary indicator dilution techniques. European Journal of Anaesthesiology. 2002. (UI 12510905).
**AE, N<500**

Della RG, Costa MG, Pompei L, Coccia C, Pietropaoli P. Continuous and intermittent cardiac output measurement: pulmonary artery catheter versus aortic transpulmonary technique.. British Journal of Anaesthesia. 2002. (UI 11990265).
**AE, N<500**

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**AE, N<500**

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# Appendix E. Forest plot data (Figures 1-3)

Figure 1. Metaanalysis of odds ratio of death, PAC vs. control.

| Category/Study | n/N (PAC) | n/N (Control) | OR | 95% Confidence Interval | Setting | Quality | Applicability |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| PAC vs. no PAC | | | | | | | |
| ESCAPE (2005) | 10/206 | 11/207 | 0.91 | (0.4, 2.2) | CCU | A | M |
| Harvey (2005) | 346/506 | 333/507 | 1.13 | (0.9, 1.5) | MICU | A | W |
| Rhodes (2002)* | nd/96 | nd/105 | 0.96 | (0.5, 1.8) | ICU | A | W |
| Richard (2003) | 119/338 | 208/348 | 0.93 | (0.7, 1.3) | ICU | A | M |
| Guyatt (1991) | 10/16 | 9/17 | 1.48 | (0.4, 5.9) | M/SICU | C | M |
| Sandham (2003) | 78/997 | 77/997 | 1.01 | (0.7, 1.4) | SICU | A | M |
| Berlauk (1991) | 1/68 | 2/21 | 0.14 | (0.0, 1.7) | SICU | B | N |
| Valentine (1998) | 3/60 | 1/58 | 3.00 | (0.3, 29) | SICU | B | N |
| Bonazzi (2002) | 0/50 | 0/50 | 1.00 | (0.0, 51) | SICU | B | N |
| | | | | | | | |
| Pooled | | | 1.03 | (0.9, 1.2) | | | |
| | | | | | | | |
| PAC vs. CVP | | | | | | | |
| Schultz (1985) | 1/35 | 10/35 | 0.07 | (0.0, 0.6) | ICU | C | M |
| NHLBI (2006) | 141/513 | 128/487 | 1.06 | (0.8, 1.4) | ICU | A | N |
| Shoemaker (1988) | 10/30 | 7/30 | 1.64 | (0.5, 5.1) | SICU | B | N |
| Pearson (1989) | 2/198 | 0/41 | 1.06 | (0.1, 22) | SICU | C | M |
| Bender (1997) | 1/51 | 1/53 | 1.04 | (0.1, 17) | SICU | B | N |
| Isaacson (1990) | 1/49 | 0/53 | 3.31 | (0.1, 83) | SICU | B | N |
| | | | | | | | |
| Pooled | | | 0.96 | (0.5, 2.0) | | | |
| | | | | | | | |
| Overall | | | 1.03 | (0.9, 1.2) | | | |

Figure 2. Metaanalyses of mean difference in hospital length of stay (LOS), PAC vs. control.

| Category/Study | LOS days (PAC) | LOS days (Control) | Difference Hospital LOS (days) | 95% Conf. Interval | Setting | Quality | Applicability |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| PAC vs. no PAC | | | | | | | |
| ESCAPE (2005) | 9 | 8 | 0.4 | (-1.4, 2.2) | CCU | A | M |
| Richard (2003) | 14 | 14 | -0.4 | (-2.1, 1.3) | ICU | A | M |
| Guyatt (1991) | 10 | 8 | -2.2 | (-10, 5.8) | M/SICU | C | M |
| Sandham (2003) | 10 | 10 | | (-1.2, 1.2) | SICU | A | M |
| Bonazzi (2002) | 12 | 11 | 1 | (-0.6, 2.6) | SICU | B | N |
| Valentine (1998) | 13 | 13 | 0 | (-5.5, 5.5) | SICU | B | N |
| Berlauk (1991) | 19 | 15 | 3.5 | (-3.3, 10) | SICU | B | N |
| | | | | | | | |
| Pooled | | | | 0.24 (-0.5, 1.0) | | | |
| | | | | | | | |
| PAC vs. CVP | | | | | | | |
| Bender (1997) | 13 | 12 | 0.5 | (-3.2, 4.2) | SICU | B | N |
| Shoemaker (1988) | 25 | 22 | 3 | (-5.6, 11) | SICU | B | N |
| Isaacson (1990) | 10 | 9 | 0.8 | (-2.2, 3.8) | SICU | B | N |
| | | | | | | | |
| Pooled | | | 0.84 | (-1.4, 3.1) | | | |
| | | | | | | | |
| Overall | | | 0.30 | (-0.4, 1.0) | | | |

Figure 3. Metaanalyses of mean difference in ICU length of stay, PAC vs. control.

| Category/Study | LOS days (PAC) | LOS days (Control) | Difference Hospital LOS (days) | 95% Conf. Interval | Setting | Quality | Applicability |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| PAC vs. no PAC | | | | | | | |
| Richard (2003) | 12 | 12 | -0.30 | (-1.8, 1.2) | ICU | A | M |
| Valentine (1998) | 8 | 7 | 1 | (-1.7, 3.7) | SICU | B | N |
| Berlauk (1991) | 3 | 3 | 0.6 | (-0.6, 1.8) | SICU | B | N |
| | | | | | | | |
| Pooled | | | 0.33 | (-0.6, 1.2) | | | |
| | | | | | | | |
| PAC vs. CVP | | | | | | | |
| Wheeler (2006) | 16 | 16 | -0.5 | (-0.8, 0.8) | ICU | A | N |
| Pearson (1989) | 2 | 1 | 0.65 | (-0.4, 1.7) | SICU | C | M |
| Bender (1997) | 3 | 3 | 0.1 | (-1.0, 1.1) | SICU | B | N |
| Shoemaker (1988) | 16 | 12 | 4.3 | (-2.6, 11) | SICU | B | N |
| Isaacson (1990) | 2 | 3 | -0.6 | (-1.4, 0.2) | SICU | B | N |
| | | | | | | | |
| Pooled | | | -0.07 | (-0.7, 0.6) | | | |
| | | | | | | | |
| Overall | | | 0.0 | (-0.5, 0.5) | | | |