Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department with Acute Heart Failure Syndromes

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This clinical policy focuses on critical issues in the evaluation and management of adult patients presenting to the emergency department (ED) with suspected heart failure. The medical literature was reviewed for articles pertaining to the critical questions posed. Subcommittee members supplied additional articles believed to have direct bearing on this policy. This clinical policy focuses on the following 4 critical questions that

were determined by the committee members to represent some of the most important and controversial issues related to the evaluation and management of adult patients who present to the ED with symptoms suggestive of acute heart failure.

1. Does a B-type natriuretic polypeptide (BNP) or NT-ProBNP measurement improve the diagnostic accuracy over standard clinical judgment in the assessment of possible acute heart failure syndromes in the ED?
2. Is there a role for noninvasive positive-pressure ventilatory support in the ED management of patients with acute heart failure syndromes and respiratory distress?
3. Should vasodilator therapy (eg, nitrates, nesiritide, and ACE inhibitors) be prescribed in the ED management of patients with acute heart failure syndromes?
4. Should diuretic therapy be prescribed in the ED management of patients with acute heart failure syndromes?

Recommendations for patient management are provided for each 1 of these topics based on strength of evidence (Level A, B, or C). *Level A recommendations* represent patient management principles that reflect a high degree of clinical certainty; *Level B recommendations* represent patient management principles that reflect moderate clinical certainty; and *Level C recommendations* represent other patient management strategies based on preliminary, inconclusive, or conflicting evidence, or based on panel consensus. This clinical policy is intended for physicians working in hospital-based EDs.

INTRODUCTION

Heart failure has reached epidemic proportions in the United States. Recent data from the American Heart Association (AHA) estimates that nearly 5 million individuals are living in the United States with heart failure (2.3% of the general population), and an additional 550,000 new cases are diagnosed each year.[1] In the United States, heart failure is associated with an annual death rate of 18.7% and estimated costs of $27.9 billion.[1] As the population ages and medical advances allow individuals with heart failure to live longer, the prevalence of heart failure is expected to grow.[2] It is estimated that heart failure accounts for more than 1 million hospital admissions annually, and it is the leading discharge diagnosis for all patients older than 65 years.[3]

The evaluation and management of chronic heart failure has evolved substantially over the last decade, prompting the American College of Cardiology (ACC)/AHA to issue specific guidelines in 1995, 2001, and more recently in 2005.[4] The most recent ACC/AHA guidelines define heart failure as a "complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood." Hemodynamic factors may activate the renin-angiotensin system, causing vasoconstriction, fluid retention, and sodium reabsorption. Findings in heart failure typically include varying degrees of reduced cardiac output, tissue hypoperfusion, increased pulmonary capillary wedge pressure, pulmonary congestion, and tissue edema. The resulting impaired cardiac output associated with heart failure may lead to symptoms of fatigue and dyspnea.

In 2005, the European Society of Cardiology published guidelines for the evaluation and management of patients with acute heart failure.[2] The large heterogeneity of disease among acute heart failure patients has contributed to the variability in reported definitions and terminology. As a result, it has been difficult to establish a consensus regarding the actual definition, epidemiology, pathophysiology, and therapy for acute heart failure.

Two terms have ultimately emerged to describe these patients. The term "acute decompensated heart failure" is used variably but typically describes those patients with known heart failure who experience acute or subacute worsening of their heart failure state.[2,5] The term "acute heart failure syndromes" emerged from 2004 and 2005 meetings of an international workgroup who were convened primarily to establish uniform terminology and definitions in heart failure.[6] The workgroup defined acute heart failure syndromes as the "gradual or rapid deterioration in heart failure signs and symptoms resulting in a need for urgent therapy."[6] The consensus document further stated that these symptoms primarily manifest from increased pulmonary congestion that results from elevated left ventricular filling pressures (with or without low cardiac output) and may occur in patients with normal or reduced left ventricular ejection fraction.[6] In an attempt to support the establishment of consensus, the American College of Emergency Physicians' (ACEP) Clinical Policies Committee has reviewed the current terminology and definitions and chosen to use the term "acute heart failure syndromes" as previously defined.

Various subclassification schemes for acute heart failure syndrome have been proposed.[2,6-9] However, because of the substantial heterogeneity of disease (eg, variable body fluid volumes and degrees of cardiac output) and the difficulty in distinguishing these various heart failure states clinically, the determination of a well-defined, noncontroversial subclassification of acute heart failure syndromes was not able to be generated by our committee at this time, and such subclassification was thought to be beyond the scope of this document. Still, appreciation of this heterogeneity is important in the understanding of why the evaluation and management of patients with acute heart failure syndromes is best performed on an individualized basis.

The emergency department (ED) plays a critical role in the management of acute heart failure syndromes since approximately 80% of patients hospitalized for the condition are admitted through the ED.[5] The comparison of studies to date has been made more challenging by the lack of consensus as to what outcomes are most important (eg, cardiopulmonary indices, symptom relief, length of hospitalization, or morbidity and mortality).

This policy was intended to help improve the evaluation and management of heart failure patients presenting to an ED by

answering 4 critical questions that represent current interest or controversy.

METHODOLOGY

This clinical policy was created after careful review and critical analysis of the medical literature. MEDLINE searches for articles published between January 1995 and December 2005 were performed using a combination of key words, including "heart failure," "natriuretic peptide," "vasodilator," "nitroglycerin," "nesiritide," "diuretic," "furosemide," "noninvasive ventilation," "continuous positive airway pressure (CPAP)," and "bi-level positive airway pressure (BiPAP)." Searches were limited to English-language sources. Additional articles were reviewed from the bibliographies of studies cited. Subcommittee members also supplied articles from their own knowledge and files.

The reasons for developing clinical policies in emergency medicine and the approaches used in their development have been enumerated.[10] This policy is a product of the ACEP clinical policy development process and is based on the existing literature; where literature was not available, consensus of emergency physicians was used. Expert review comments were received from individual emergency physicians and from individual members of the American College of Cardiology, American Heart Association, and American College of Chest Physicians. Their responses were used to further refine and enhance this policy. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology or the practice environment changes significantly.

All articles used in the formulation of this clinical policy were graded by at least 2 subcommittee members for strength of evidence and classified by the subcommittee members into 3 classes of evidence on the basis of the design of the study, with design 1 representing the strongest evidence and design 3 representing the weakest evidence for therapeutic, diagnostic, and prognostic clinical reports, respectively (Appendix A). Articles were then graded on 6 dimensions thought to be most relevant to the development of a clinical guideline: blinded versus nonblinded outcome assessment, blinded or randomized allocation, direct or indirect outcome measures (reliability and validity), biases (eg, selection, detection, transfer), external validity (ie, generalizability), and sufficient sample size. Articles received a final grade (Class I, II, III) on the basis of a predetermined formula taking into account design and quality of study (Appendix B). Articles with fatal flaws were given an "X" grade and not used in the creation of this policy. Evidence grading was done with respect to the specific data being extracted, and the specific critical question being reviewed. Thus, the level of evidence for any one study may vary according to the question, and it is possible for a single article to receive different levels of grading as different critical questions are answered. Question-specific level of evidence grading may be found in the Evidentiary Table included at the end of this policy.

Clinical findings and strength of recommendations regarding patient management were then made according to the following criteria:

Level A recommendations. Generally accepted principles for patient management that reflect a high degree of clinical certainty (ie, based on strength of evidence Class I or overwhelming evidence from strength of evidence Class II studies that directly address all of the issues).

Level B recommendations. Recommendations for patient management that may identify a particular strategy or range of management strategies that reflect moderate clinical certainty (ie, based on strength of evidence Class II studies that directly address the issue, decision analysis that directly addresses the issue, or strong consensus of strength of evidence Class III studies).

Level C recommendations. Other strategies for patient management that are based on preliminary, inconclusive, or conflicting evidence, or in the absence of any published literature, based on panel consensus.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as heterogeneity of results, uncertainty about effect magnitude and consequences, strength of prior beliefs, and publication bias, among others, might lead to such a downgrading of recommendations.

This policy is not intended to be a complete manual on the evaluation and management of adult patients with acute heart failure but rather a focused examination of critical issues that have particular relevance to the current practice of emergency medicine.

It is the goal of the Clinical Policies Committee to provide an evidence-based recommendation when the medical literature provides enough quality information to answer a critical question. When the medical literature does not contain enough quality information to answer a critical question, the members of the Clinical Policies Committee believe that it is equally important to alert emergency physicians to this fact.

Recommendations offered in this policy are not intended to represent the only diagnostic and management options that the emergency physician should consider. ACEP clearly recognizes the importance of the individual physician's judgment. Rather, this guideline defines for the physician those strategies for which medical literature exists to provide support for answers to the crucial questions addressed in this policy.

Scope of Application. This guideline is intended for physicians working in hospital-based EDs.

Inclusion Criteria. This guideline is intended for adult patients presenting to the ED with symptoms or signs suggestive of acute heart failure.

Exclusion Criteria. This guideline is not intended to address the care of those patients presenting with acute ST-elevation myocardial infarction, high-output heart failure,

cardiogenic shock, renal failure, valvular emergencies, or the care of pediatric patients.

CRITICAL QUESTIONS

1. Does a B-type natriuretic polypeptide (BNP) or NT-ProBNP measurement improve the diagnostic accuracy over standard clinical judgment in the assessment of possible acute heart failure syndromes in the ED?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. The addition of a single BNP or NT-proBNP measurement can improve the diagnostic accuracy compared to standard clinical judgment alone in the diagnosis of acute heart failure syndrome among patients presenting to the ED with acute dyspnea.

Use the following guidelines:

- BNP <100 pg/dL or NT-proBNP <300 pg/dL acute heart failure syndrome unlikely* (Approximate LR- = 0.1)
- BNP >500 pg/dL or NT-proBNP >1,000 pg/dL acute heart failure syndrome likely (Approximate LR+ = 6)

Level C recommendations. None specified.

BNP is produced by cardiac myocytes in response to increased end-diastolic pressure and volume, as occurs in the setting of heart failure. Pre-proBNP is synthesized within myocytes and cleaved to proBNP. The latter is released into the circulation and then cleaved to the active BNP and an inactive N-terminal fragment, called NT-proBNP. During the past decade, both BNP and NT-proBNP have been studied as markers for aiding in the diagnosis of acute heart failure syndrome in patients presenting with dyspnea in the acute setting. Although BNP is a rapidly transcribed protein in the body, animal data suggest that BNP levels may lag an hour or more behind the clinical picture.[11,12]

In 2 studies derived from the same sample by Maisel et al[13] and McCullough et al,[14] the measuring of BNP values among patients presenting with dyspnea was believed to improve accuracy in the diagnosis of patients with acute heart failure. The largest trial to date is a Class II, industry-sponsored, prospective, multicenter, observational study that enrolled 1,586 subjects with a primary complaint of "shortness of breath" and compared a single BNP measurement (Triage; Biosite Inc, San Diego, CA) against a criterion-standard, final diagnosis as determined retrospectively by 2 cardiologists blinded to BNP levels.[13] Subjects with advanced renal failure (CrCl <15 mL/min) were excluded. All subjects in whom acute dyspnea was adjudicated to be due to a cause other than acute heart failure syndrome, regardless of the presence or absence of underlying left-ventricular dysfunction, were considered as a single group. Using a cut point of 50 pg/mL, BNP measurements predicted a final diagnosis of acute heart failure syndrome with a sensitivity of 0.97 and a specificity of 0.62. A cut point of 100 pg/mL yields a sensitivity of 90% and specificity of 76%. Higher cut points resulted in improved specificity, up to 0.90 at a cut point of 1,000 pg/mL, but at the expense of markedly lower sensitivity. The overall area under the receiver operating characteristic (ROC) curve for this test was calculated as 0.91.† The authors' assumption that the costs associated with false negatives tend to outweigh the costs associated with false positives leads to the selection of a relatively low cut point (ie, 80 to 100 pg/mL) in clinical practice.[15] In data derived from the same sample population, McCullough et al[14] reported on 1,538 subjects for whom the clinical likelihood of acute heart failure syndromes was recorded by an emergency physician who was blinded to the BNP level. In this study, the area under the curve (AUC) for "estimated congestive heart failure probability" based on clinical evaluation alone was 0.86, as compared to 0.90 for a single BNP measurement, and 0.93 for the combination of clinical evaluation and BNP.

Comparisons such as these may be limited by the uncertainty of whether the retrospectively defined "criterion standard" is, in fact, more accurate than a real-time, clinical diagnosis by an attending emergency physician. Another issue in interpreting these data has to do with generalizability, as this population was a convenience sampling of subjects with a "primary complaint of dyspnea," but excluded individuals with dyspnea "clearly not secondary to congestive heart failure." In this trial, a relatively low proportion of subjects (72/1,586) had underlying left ventricular dysfunction with dyspnea that was due to a noncardiac cause. In practice, these may be the most challenging patients to classify clinically.

Age, body mass index, and renal function may influence BNP and NT-proBNP measurements.[15-21] Several post hoc analyses have shown that BNP measurements may retain discriminatory power in various subpopulations, including individuals with systolic and diastolic heart failure,[16] underlying pulmonary disease,[17] advanced renal disease,[18] older age,[15] and obesity.[19] However, more research is necessary to better understand the direction and magnitude of these effects to provide further specific guidance in the interpretation of results.

Numerous smaller, Class II[12,22] and Class III[23-26] single-center trials of BNP measurements for the diagnosis of acute heart failure syndrome in the acute setting have been conducted and reported similarly high AUC (range: 0.82 to 0.99) for a single BNP measurement as against a variety of clinical criterion-standard criteria for the diagnosis of acute heart failure syndrome. Most of these have studied the same point-of-care test (Triage, Biosite). Ray et al[22] is the only study that rigorously defined a cohort of patients with acute severe dyspnea, and reported an AUC of 0.87 for a single BNP measurement.

*BNP conversion: 100 pg/mL=22 pmol/L; NT-proBNP conversion: 300 pg/mL=35 pmol/L

†An ROC curve is a graphic representation of the tradeoff between sensitivity and specificity for every possible cutoff. The closer the AUC is to 1.0, the better the test is, and the closer the AUC is to 0.5, the worse the test is.

BNP is one of the few diagnostics available in the ED setting that has been subjected to outcomes testing. A single BNP measurement is associated with reductions in treatment costs and time to discharge among patients presenting to the ED with acute severe dyspnea. In a single-center, prospective, randomized trial, Mueller et al[27] enrolled 452 consecutive adults presenting to the ED with severe dyspnea as their primary symptom, and randomized subjects to rapid, bedside BNP measurement (Triage, Biosite) versus standard clinical evaluation. Subjects with significant renal disease (Cr >2.8 mg/dL) were excluded. The use of BNP measurement was associated with statistically significant improvements in both of the study's primary outcome measure: median time to discharge (8 days versus 11 days) and mean total treatment cost ($5,410 versus $7,264). Chronic obstructive pulmonary disease was more likely to be diagnosed in the "BNP measurement" group, and approximately one-third of the cost savings was associated with finding an alternative diagnosis to acute heart failure syndrome. In post hoc subgroup analyses, these results were corroborated among female subjects but not among those with kidney disease (glomerular filtration rate [GFR] <60 mL/min).[28,29]

NT-proBNP has not been studied quite as extensively as BNP for the diagnosis of acute heart failure syndromes but has rendered results similar to that previously reported for BNP. The largest published trial was a Class II prospective, industry-supported, single-center, observational trial that enrolled a convenience sampling of 600 subjects with a complaint of dyspnea, excluding those with significant renal insufficiency (Cr >2.5 mg/dL), and any subject who had an unblinded NP measurement.[20] A single NT-proBNP measurement (Elecsys 2010; Roche Diagnostics, Indianapolis, IN) was compared against a criterion standard, final adjudicated diagnosis. Using a cut point of 300 pg/mL, NT-proBNP measurements predicted a final diagnosis of acute heart failure syndrome with a sensitivity of 0.99 and a specificity of 0.68. At a cut-point of 1,000 pg/ml, the sensitivity was 0.87 and the specificity was 0.86. The overall AUC for NT-proBNP measurement was calculated as 0.94. The corresponding AUC for the attending emergency physicians' "clinical judgment" was also quite high (0.90), perhaps reflecting an artifact of subject sampling (ie, subjects with unclear diagnoses may have been selectively excluded because they were more likely to have nonblinded natriuretic peptide measurements performed). A smaller study of NT-proBNP measurement in the ED setting has also produced similar results.[30] As in the case with BNP, factors such as advancing age, obesity, and renal dysfunction influence the optimal cut point for discriminating between cardiac and noncardiac causes of dyspnea.[20,21]

BNP measurement and NT-proBNP measurement have been compared head to head in a number of prospective trials that have found that these 2 tests correlate with essentially parallel ROC curves and statistically similar AUCs with respect to the diagnosis of acute heart failure syndrome.[31-34] One well-designed Class II study with 251 consecutive ED patients and strict inclusion/exclusion criteria calculated AUCs of 0.92 and 0.90 for BNP (AxSYM; Abbot Laboratories, Irving, TX) and NT-proBNP (Elecsys 2010, Roche) respectively.[32]

2. Is there a role for noninvasive positive-pressure ventilatory support in the ED management of patients with acute heart failure syndromes and respiratory distress?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Use 5 to 10 mm Hg CPAP by nasal or face mask as therapy for dyspneic patients with acute heart failure syndrome without hypotension or the need for emergent intubation to improve heart rate, respiratory rate, blood pressure, and reduce the need for intubation, and possibly reduce inhospital mortality.

Level C recommendations. Consider using BiPAP as an alternative to CPAP for dyspneic patients with acute heart failure syndrome; however, data about the possible association between BiPAP and myocardial infarction remain unclear.

Although the majority of patients with acute heart failure syndrome respond well to medical therapy, some patients will require ventilatory assistance.[35] Noninvasive ventilatory assistance may be provided by either CPAP or BiPAP. CPAP provides a constant, positive, end-expiratory airway pressure, whereas BiPAP provides the same constant end-expiratory pressure, as well as added positive pressure at the onset of inspiration to assist ventilation. CPAP and BiPAP devices typically attach to the patient by a nasal or face mask. By improving oxygenation, reducing respiratory work, and decreasing left ventricular afterload, the positive airway pressure provided by these devices has been thought to improve pulmonary mechanics and hemodynamics, as well as reduce the need for endotracheal intubation, hospital length of stay, and mortality.

Although comparison of studies of noninvasive ventilatory assistance in acute heart failure syndrome is made more difficult by variability in study inclusion criteria, medical management, and in CPAP administration, initial studies evaluating CPAP by either nasal or face mask at 5 to 10 mm Hg consistently showed significant improvements in oxygenation, reductions in heart rate, reductions in respiratory rate, and reductions in blood pressure compared with standard oxygen therapy.[36-43] Several of these studies also reported statistically significant improvements in cardiopulmonary indices (eg, pulmonary capillary wedge pressure, stroke volume, cardiac output, or cardiac index),[39,40] as well as a reduction in the rate of intubation.[37,38,40,43] With the exception of one study that showed a reduction in mortality,[44] a statistically significant benefit over standard oxygen therapy has not been found by investigators who have evaluated the effect of CPAP on the hospital length of stay and mortality.[36-38,40,43,45,46] However, the magnitude and direction

of the mortality effects in these studies generally favor CPAP, suggesting the possibility that there may be a small benefit that these studies were too underpowered to detect.[36-38,40,43,45,46]

In one of the largest, prospective, randomized, controlled, Class I studies, L'Her et al[44] evaluated 89 consecutive, elderly patients with acute hypoxemic respiratory failure (ie, $PaO_2/FiO_2 \leq 300$) resulting from cardiogenic pulmonary edema. The study intended to enroll 180 subjects but was suspended prematurely after an interim analysis revealed that patients randomized to receive face mask CPAP at 7.5 mm Hg had significantly less need for BiPAP or endotracheal ventilatory assistance, as well as lower 48 hour mortality compared with those receiving standard mask oxygen therapy. Although patient severity of disease appeared comparable between the 2 study groups, the need for ventilatory assistance was 17% less ($P=0.01$) in the CPAP group (7%) compared to those receiving standard oxygen therapy (24%). Additionally, early 48-hour mortality was 21% less ($P=0.017$) in the CPAP group (9%) compared to those receiving standard oxygen therapy (30%). Still, no difference was found in the hospital length of stay.

Experiences using BiPAP for patients with acute heart failure were first reported in the literature in the mid to late 1990s.[47-51] These studies were typically small, and the findings were variable as to whether BiPAP afforded any additional benefit over standard therapy. In a 1997 Class III study, Mehta et al[52] reported a trial comparing BiPAP, CPAP, and conventional oxygen therapy for patients with acute heart failure syndrome. BiPAP was no more efficacious than CPAP, and may have been associated with a higher rate of myocardial infarction as defined by elevated cardiac markers. The study was halted after the enrollment of 27 patients when an interim analysis found that the rate of myocardial infarction was higher in the BiPAP group (71%, N=10, $P=0.06$) compared with those receiving CPAP (31%, N=4). However, these results are questionable because the severity of illness among patients in the BiPAP group may have been greater than among those receiving other therapies (ie, selection bias), statistical significance resulted only after a patient who signed consent late was included, and the 95% confidence intervals (CIs) were extremely large (ie, 9% to 76%) because of the small sample size. No statistically significant differences were detected among treatment strategies for the rate of intubation, intensive care unit length of stay, hospital length of stay, or mortality.

Subsequently, 3 Class III, prospective, randomized trials have evaluated the benefit of BiPAP compared to a control group of conventional oxygen therapy for patients with acute heart failure syndrome, and only 1 of the 3 reported benefit.[53-55] Although it is still unclear what effect BiPAP may have on the rates of intubation and myocardial infarction in acute heart failure syndrome, it has not yet reliably been shown to improve oxygenation or hemodynamics compared with conventional oxygen therapy.

In a 2000 study of BiPAP, Masip et al[53] evaluated 37 patients and reported significantly less intubation (5% BiPAP versus 33% control; $P=0.04$) and faster time to resolution of symptoms (ie, oxygen saturation $\geq$ 96% and respiratory rate $<$30 breaths/min) in the BiPAP group. Ultimately, this study was weakened by the fact that the study was small, the control group was sicker, and the patients were not all from the ED.

Sharon et al[54] reported the findings of consecutive patients who were randomized to receive either BiPAP and standard nitrate therapy or the control of conventional oxygen by mask and high-dose nitrate therapy in the out-of-hospital setting. The BiPAP arm was associated with an increased incidence of intubation, myocardial infarction, and the combined endpoint of death, need for mechanical ventilation, or myocardial infarction within 24 hours of admission. However, because of the differences in nitrate dosing between the 2 groups, it is impossible to know whether the worse outcome associated with the administration of BiPAP was attributable to the BiPAP alone, lower dose nitrate therapy, or both.

In the third study by Levitt[55] in 2001, a convenience sample of 38 patients randomized to receive BiPAP or conventional oxygen therapy revealed no statistically significant difference in heart rate, respiratory rate, oxygenation, rate of intubation, or hospital length of stay between treatment arms. However, there was also no difference in the rate of myocardial infarction.

Since the Mehta et al[52] study in 1997, 2 studies have directly compared CPAP and BiPAP for patients with acute heart failure syndrome, and in these studies, neither modality was found to be superior to the other.[56,57]

Chadda et al[56] in 2002 performed a small, Class III, prospective, crossover study of 6 patients with acute heart failure who were sequentially treated with CPAP 5 mm Hg, CPAP 10 mm Hg, and finally BiPAP 10/5 mm Hg. Although the work of breathing decreased while patients received BiPAP, there was no significant difference in oxygenation or hemodynamic response between the different therapies.

In a head-to-head, Class II study, Bellone et al[57] in 2004 prospectively randomized 46 patients with acute heart failure to receive CPAP at 10 mm Hg or BiPAP at 15/5 mm Hg. No differences were found in the rate of myocardial infarction, rate of intubation, or inhospital mortality between treatment groups. This study lacked statistical power to detect a difference in the rate of myocardial infarction. Additionally, these findings should not be generalized to those patients with acute heart failure thought to also be experiencing acute coronary syndrome because such patients were excluded from the analysis.

3. Should vasodilator therapy (eg, nitrates, nesiritide, and ACE inhibitors) be prescribed in the ED management of patients with acute heart failure syndromes?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Administer intravenous nitrate therapy to patients with acute heart failure syndromes and associated dyspnea.

Level C recommendations.

1. Because of the lack of clear superiority of nesiritide over nitrates in acute heart failure syndrome and the current uncertainty regarding its safety, nesiritide generally should not be considered first line therapy for acute heart failure syndromes.
2. Angiotensin-converting enzyme (ACE) inhibitors may be used in the initial management of acute heart failure syndromes, although patients must be monitored for first dose hypotension.

Nitrates

The results of 3 Class II studies suggested that nitroglycerin is effective in acute heart failure.[58,59,60] In a Class II, prospective, randomized, unblinded investigation by Cotter et al,[58] high-dose nitrates (ie, 3 mg IV isosorbide dinitrate every 5 minutes) used with low-dose furosemide (ie, 40 mg IV) was a more effective treatment regimen in acute heart failure than low-dose nitrates (ie, 1 mg/hour IV isosorbide dinitrate) and high-dose furosemide (ie, 80 mg IV every 15 minutes). In this trial, 104 patients with severe, acute heart failure were treated by physicians in the out-of-hospital setting with 1 of 2 treatment approaches. The group that received high-dose nitrates had significantly fewer myocardial infarctions (37% versus 17%) and intubations (40% versus 13%). A significant number of subjects were excluded from randomization and not compared to the study group, hence introducing the possibility of selection bias. Despite limitations, this study suggests that high-dose nitrates used in combination with low-dose furosemide is a more effective treatment regimen in acute heart failure than low-dose nitrates when combined with high-dose furosemide. The cohort in this study was not stratified for heart failure type (ie, fluid overload versus pump failure).

The second Class II study was a retrospective analysis of registry data from 65,180 patients with acute heart failure syndromes, of whom 6,549 patients received intravenous nitroglycerin therapy.[60] Treatment with intravenous nitroglycerin significantly reduced inhospital mortality compared with that of patients who received inotropic therapy with either milranone (odds ratio [OR] 0.69; 95% CI 0.53 to 0.89) or dobutamine (OR 0.46; 95% CI 0.37 to 0.57). After controlling for differences in baseline characteristics by covariate analysis, no difference in mortality was found in a direct comparison between nitroglycerin and nesiritide (OR 0.94; 95% CI 0.77 to 1.16).

The Vasodilation in the Management of Acute Congestive heart failure (VMAC) trial, described under the Nesiritide section, also evaluated nitroglycerin in acute heart failure syndrome.[59] In this Class II study, dyspnea scores and global clinical status scores in the nitroglycerin group did not differ significantly from either nesiritide or placebo during the first 3 hours of therapy. However, nitroglycerin significantly lowered mean pulmonary vascular resistance compared to placebo at 1 hour and significantly lowered mean right atrial pressure compared to placebo at 3 hours. Intravenous nitroglycerin mean dosing was 42 μg per minute for catheterized patients and 29 μg per minute for noncatheterized patients. Standard therapy was not determined *a priori*.

Nesiritide

Nesiritide is a recombinant form of B-type (brain) natriuretic peptide that dilates veins, peripheral arteries, and coronary arteries. As a result, nesiritide reduces preload and afterload and has been studied in acute heart failure syndromes.

Several prospective, randomized, placebo-controlled trials have evaluated nesiritide in acute heart failure syndromes.[59,61-63] These studies demonstrated that nesiritide is significantly more effective than placebo in treating patients with acute heart failure syndromes.

Mills et al[62] demonstrated that nesiritide, compared to placebo, significantly decreased pulmonary capillary wedge pressure (27% to 39%) and significantly increased cardiac index within the first 6 hours of acute heart failure treatment. This Class I, prospective, clinical trial measured indirect outcomes.

Colucci et al[63] compared escalating doses of nesiritide to placebo during the first 6 hours of acute heart failure syndrome treatment. Study patients did not receive oral or intravenous medications other than nesiritide during the 6-hour study period. Nesiritide significantly improved pulmonary capillary wedge pressure, global clinical status, dyspnea, and fatigue compared to placebo. Even though the overall Colucci et al[63] study is Class III quality, data from the first 6 hours of treatment are Class II. In the nonblinded 7-day portion of the Colucci et al[63] study, nesiritide's beneficial effects continued compared to "standard therapy," which was left to the discretion of the individual physicians.

Abraham et al[61] compared escalating doses of nesiritide to placebo in 16 human subjects. This prospective, double blind, randomized clinical trial was underpowered and had probable treatment bias. Two of 16 subjects (12.5%) were excluded from the data analysis because of severe hypotension in one patient and an apparent allergic reaction in another. Nevertheless, this Class III study found that nesiritide significantly improved cardiac index and significantly lowered right atrial pressure, pulmonary capillary wedge pressure, and systemic vascular resistance compared with baseline. Mean arterial pressure was significantly lower in the nesiritide group compared with baseline.

The VMAC group compared placebo, nesiritide, and nitroglycerin therapies.[59] All 3 arms received unspecified "standard" therapy for 3 hours and were randomized after this 3-hour period to placebo, intravenous nesiritide, or intravenous nitroglycerin. Intravenous nitroglycerin was administered at a lower, likely suboptimal dose (ie, 29 to 42 μg/min). The authors identified a 2 mm Hg mean difference in pulmonary capillary wedge pressure reduction between the nesiritide and nitroglycerin groups. This mean difference in pulmonary capillary wedge pressure between the therapies was statistically significant; however, it is unclear whether this difference has clinical impact. After 3 hours of therapy, dyspnea in the

nesiritide group was significantly improved when compared only to placebo but not nitroglycerin. Although nesiritide is more effective than placebo, its efficacy compared with nitroglycerin is less clear.

In a Class III prospective study, Burger et al[64] found significantly more dysrhythmias in the dobutamine-treated patients compared to nesiritide. However, this study was not blinded, "standard therapy" was not controlled throughout the study, and the methodology had selection bias and treatment bias.

Recently, 2 meta-analyses questioned the safety of nesiritide in the treatment of patients with acute heart failure.[65,66] In the Class I study by Sackner-Bernstein et al[66] the authors analyzed pooled data from 3 prospective clinical trials evaluating nesiritide in acute heart failure.[59,63,67] Data were extracted from FDA documents, sponsor documents, and published peer review studies (N=862 subjects). The included papers all used 6-hour nesiritide infusions, control groups without vasopressors, and evaluated 30-day mortality. Based on this analysis, it appeared that there may have been greater mortality in the nesiritide group.

The same authors published a Class II meta-analysis suggesting nesiritide increases serum creatinine levels.[65] This study analyzed 5 prospective, randomized, clinical trials (N=1,269 patients). Compared with control subjects who did not receive inotrope therapy (ie, received diuretics and vasodilators), subjects who received nesiritide had increased risk of worsening renal function (nesiritide dose 0.03 μg/kg/min: relative risk 1.52; 95% CI 1.16 to 2.0; nesiritide dose 0.015 μg/kg/min: relative risk 1.46; 95% CI 1.09 to 1.95). The rate of medical interventions among nesiritide patients was 11.9% compared with 4.2% in the control group. There was no significant difference between nesiritide and control in terms of the need for dialysis. However, this meta-analysis did not provide an assessment of the quality or validity of the individual trials. Moreover, there was no description of the individual trial sites or participants that would allow for an assessment in appropriateness of combining data from these studies. Tests for heterogeneity were low powered.

To help elucidate the potential risk of nesiritide in acute heart failure, Abraham[68] performed a pooled analysis of 7 randomized clinical trials of nesiritide. The common endpoints were mortality at 30 and 180 days. The author generated hazard ratios for mortality related to nesiritide use. The pooled hazard ratio for nesiritide compared to placebo for 30-day mortality was 1.27 (95% CI 0.81 to 2.01). This study was limited by the small number of deaths at 30 days and the differing treatment regimens among the publications studied.

Data from the ADHERE registry demonstrated that both nitroglycerin and nesiritide were equally associated with significantly less inhospital mortality compared to inotropic therapy with either milranone or dobutamine for patients requiring hospitalization for acute heart failure syndrome. Although nitroglycerin was initially found to be associated with significantly less inhospital mortality compared with nesiritide, both therapies appeared equal after controlling for differences in baseline characteristics on covariate analysis.

In 2005, an industry-sponsored expert panel reviewed data related to possible adverse effects associated with nesiritide. The panel determined that there was insufficient data to make recommendations regarding adverse effects directly attributable to nesiritide, and stated that further investigation was necessary (http://www.sciosinc.com/scios/pr_1118721302).

ACE Inhibitors

ACE inhibitors interrupt the renin-angiotensin system and lead to decreased preload and decreased afterload. However, no adequately powered, controlled, randomized clinical trials exist that evaluate the efficacy of ACE inhibitors in acute heart failure syndromes. Verma et al[69] randomized 36 subjects with acute heart failure syndromes to enalapril, nitrates, or doxazosin. Enalapril significantly decreased mean pulmonary capillary wedge pressure compared with baseline (ie, 6 to 7 mm Hg mean decrease). This underpowered study had poor generalizability (ie, all patients had evidence of acute coronary syndrome), lack of a placebo arm, and single-blinded methodology.

Several Class II and Class III studies[70-74] reported first dose hypotension in acute heart failure patients receiving oral ACE inhibitors. Four of these studies measured hemodynamics as primary outcomes in prospective studies.[71-74] Agusti et al[70] conducted a meta-analysis of 51 studies in which hemodynamics were not the primary outcomes. Anthopolous et al[71] reported an average decrease in mean arterial pressure after ACE inhibitor of 17.6$\pm$8.3 mm Hg. Vitovec et al[74] reported an average decrease in mean arterial pressure of 21$\pm$12 mm Hg. Podbregar et al[73] noted occasional symptomatic hypotension (eg, a change from 124/75 mm Hg to 65/28 mm Hg in 1 patient), although this phenomenon was not found in the larger Vitovec et al[74] study of 298 subjects with heart failure.

4. Should diuretic therapy be prescribed in the ED management of patients with acute heart failure syndromes?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Treat patients with moderate-to-severe pulmonary edema resulting from acute heart failure with furosemide in combination with nitrate therapy.

Level C recommendations.

1. Aggressive diuretic monotherapy is unlikely to prevent the need for endotracheal intubation compared with aggressive nitrate monotherapy.
2. Diuretics should be administered judiciously, given the potential association between diuretics, worsening renal function, and the known association between worsening renal function at index hospitalization and long-term mortality.

Over the years, physicians have been reassured by their bedside observations that loop diuretics (eg, furosemide, bumetanide, and torsemide) appear to be effective in the treatment of patients with heart failure by increasing urine output and decreasing edema. This easily measured short-term effect has led to the assumption that diuretic therapy also improves both index hospitalization and long-term clinical outcomes. Currently, there are no randomized clinical trials evaluating the clinical benefit of furosemide alone in acute heart failure syndromes.

In a small case series of patients with advanced chronic heart failure, Francis et al[75] determined that patients receiving furosemide transiently experienced worsening hemodynamics. This study included 15 clinically stable patients with advanced chronic heart failure and no pulmonary edema. Patients received invasive hemodynamic monitoring and were then administered furosemide 1.3±0.6 mg/kg intravenously. During the next 1 to 2 hours, the patients receiving lasix experienced worsening hemodynamics, including increased systemic vascular resistance, increased left ventricular filling pressures, and a resultant decrease in stroke volume. Other Class II and III studies have similarly reported improved hemodynamics after nitrate administration and transiently worsening hemodynamics for 1 to 2 hours after treatment with furosemide.[76-79] The generalizability of these findings to the acute care setting remains uncertain.

After these investigations, 2 clinical studies concluded that loop diuretic monotherapy may not improve short-term ED outcomes (ie, improve hemodynamic status, patient dyspnea, and reduce rate of endotracheal intubation) among patients presenting with moderate-to-severe acute pulmonary edema.

In a small, nonblinded, Class III trial of 57 out-of-hospital patients who received treatment, Hoffman and Reynolds[80] assessed the rates of clinical improvement with various combinations of nitrates, morphine, and furosemide administered in the out-of-hospital setting. The study demonstrated that the combination of nitrate and furosemide therapy was associated with the highest frequency of clinical improvement, and this benefit was believed most attributable to the nitrate.[80]

In the only clinical study identified that recruited patients with acute pulmonary edema and moderate-to-severe respiratory distress, Cotter et al[58] reported reduced rates of the composite outcome of hospital death, myocardial infarction, and intubation among the patients receiving higher-dose nitrate therapy in the out-of-hospital setting. In this study, 104 patients with acute heart failure syndrome were randomized by physicians working in the field with emergency medical services in Israel to receive either low-dose furosemide and high-dose nitrates or high-dose furosemide and low-dose nitrates. Most of the study subjects had a history of chronic heart failure, and there were no patients included with acute ST-elevation myocardial infarction. All enrolled patients had rales on chest examination and a room air pulse oximetry of less than 90% when sitting upright. However, one study arm used high-dose nitrates (8-fold difference between study arms) and the other arm used high-dose furosemide (4-fold difference between study arms). The combined endpoint of hospital death, myocardial infarction within 24 hours, and intubation within 12 hours was significantly lower in the high-dose nitrate group (25% versus 46%; $P<0.04$). Most significant was the endotracheal intubation rate difference within the first 12 hours, with the high-dose nitrate treated patients requiring much less intubation than those receiving high-dose furosemide (13% versus 40%, $P<0.005$). Additionally, significantly more patients were diagnosed with myocardial infarction within the first 24 hours of admission in the high-dose furosemide group than the high-dose nitrate group (37% and 17%, respectively, $P<0.05$).

Potential safety considerations regarding diuretic administration were raised in a Class III study that demonstrated an association between diuretic use and worsening renal function.[81] In this multicenter, nested, case-control study of 382 patients, worsening renal function was associated with a 60 mg greater total dose of furosemide the day before compared with those who did not develop worsening renal function (199 mg±195 versus 143 mg±119; $P< 0.05$).[81] This association suggests caution is warranted when dosing furosemide; however, it does not prove causality because higher-dose diuretic administration may be a surrogate marker for more advanced heart failure.

The possible association of diuretics with worsening renal function is important, given that several recent studies have identified an association between impaired renal function and increased mortality among acute heart failure syndrome patients. Data from more than 60,000 patients in the ADHERE registry show that in-hospital mortality is greater than 20% among patients with an admission blood urea nitrogen level greater than 43 mg/dL, a creatinine level greater than 2.7 mg/dL, and a systolic blood pressure less than 115 mm Hg.[82] In a retrospective study of 1,681 patients younger than 65 years of age who were admitted for acute heart failure syndromes, Krumholz et al[83] showed that an increase in the serum creatinine level of greater than 0.3 mg/dL during the index hospitalization was associated with a nearly 3 times greater risk of inhospital mortality (OR 2.7, 95% CI 1.6 to 4.6) among patients with acute heart failure syndromes. Furthermore, in a prospective cohort study of 412 hospitalized patients with acute heart failure syndrome, Smith et al[84] demonstrated a stepwise increase in 6-month mortality as serum creatinine increased from greater than or equal to 0.1mg/dL to greater than or equal to 0.5 mg/dL above baseline.

Given the heterogeneity of patients with acute heart failure syndromes, the "best dose" of diuretic is likely to be different for each patient. In the absence of clear safety data, it seems reasonable to propose that diuretic therapy, when prescribed, requires careful titration to promote effective diuresis while avoiding worsening renal function.

Future Areas of Research

Patients presenting to EDs with acute heart failure syndromes are a unique group that may require both evaluation and treatment that differs from that of patients with chronic heart failure presenting to primary care physicians. Future studies in the diagnostic performance of natriuretic peptides should focus on the utility of natriuretic peptide determinations combined with real-time clinical assessment. Further, prospective studies on the efficacy and safety of vasodilator therapy in acute heart failure syndromes are needed. Studies of diuretics in acute heart failure syndromes are still needed that more clearly evaluate the efficacy and safety directly attributable to their administration.

Relevant industry relationships are those relationships with companies associated with products that significantly impact the specific aspect of disease addressed in the critical questions.

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Evidentiary Table.

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Logeart et al[12]	2002	Prospective, single center, observational; N=163	Inclusion: patients presenting to the ED with acute severe dyspnea; Exclusion: acute myocardial infarction; chest injury; recent surgery; treatment started >2 h before arrival; emergency ECHO not feasible; BNP measurement: triage (Biosite); doppler ECHO within 60 min after inclusion	Final diagnosis determined by 2 cardiologists and 1 pulmonologist blinded to BNP and ECHO results; CHF vs non-CHF (including acute primary lung disorders with or without underlying LV dysfunction)	Final diagnoses CHF: 115 Non-CHF: 48; Cut point 100 pg/mL; sensitivity 96%, specificity 31%; Cut point 200 pg/mL; sensitivity 93%, specificity 56%; Cut point 300 pg/mL; sensitivity 88%, specificity 87%; AUC=0.93; Doppler ECHO LVEF 0.45; sensitivity 65%, specificity 85%; Restrictive mitral pattern on Doppler ECHO sensitivity 89%, specificity 93%	Severe dyspnea, 90% of patients were admitted to the ICU; high proportion of CHF cases; BNP assay of limited value in diagnosing CHF when blood was sampled <4 h from symptom onset (BNP <100 in 4/14 patients and <300 in 10/14)	II
Maisel et al[13]	2002	Prospective, multicenter (7 sites in US and abroad), observational; N=1,586	Inclusion: ED patients with shortness of breath as most prominent symptom; Exclusion: dyspnea "clearly not secondary to CHF" (eg, trauma), renal failure, acute MI; BNP measurement: triage (Biosite)	Independent review by 2 cardiologists blinded to BNP levels; (1) dyspnea due to CHF (2) dyspnea due to non-cardiac cause in patient with history of LV dysfunction (3) dyspnea not due to CHF; for binary analyses, groups (2) and (3) combined	Final diagnoses: (1) 744 (47%); (2) 72 (5%); (3) 770 (49%); Cut point 50 pg/mL sensitivity 0.97 specificity 0.62; Cut point 80 pg/mL sensitivity 0.93 specificity 0.74; Cut point 100 pg/mL sensitivity 0.90 specificity 0.76; Cut point 150 pg/mL sensitivity 0.85 specificity 0.83; AUC=0.91 *cut point 500 pg/mL specificity 0.87; *Cut point 1,000 pg/mL specificity 0.90; * From Knudsen CW, Clopton P, Westheim A, et al. *Ann Emerg Med.* 2005;45:573-580.	Convenience sampling; potential variability in application of exclusion criteria; few exclusions; relatively low prevalence of patients in group (2); limitation of "criterion-standard" diagnosis (11% disagreement between 2 reviewers - ranging from 0% to 24% across 7 sites); BNP assay had upper limit of 1,300 pg/mL	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
McCullough et al[14]	2002	Prospective, multicenter (7 sites in US and abroad), observational; N=1,538 (subjects who had clinical certainty of CHF determined by attending physician in the ED)	Inclusion: ED patients with primary complaint of dyspnea; Exclusion: "overt cause of dyspnea"; advanced renal failure (calculated CrCl <15 mL/min); acute MI; 1,666 subjects screened; attending emergency physician's estimate of clinical probability of CHF recorded on a visual analog scale	Reviewers blinded to emergency physicians' estimates	Cut point "80% clinical certainty" sensitivity 0.49 specificity 0.96; Cut point 100 pg/mL sensitivity 0.90 specificity 0.73; AUC clinical judgment: 0.86 BNP: 0.90 combined: 0.93; CHF probability nomogram	Concern that "criterion-standard" diagnosis may, in fact, not be more accurate as emergency physician diagnosis	II
Maisel et al[15]	2004	Prospective, multicenter (7 sites in US and abroad), observational; N=1,538 (subjects who had clinical certainty of CHF determined by attending physician in the ED)	Inclusion: ED patients with primary complaint of dyspnea; Exclusion: "overt cause of dyspnea"; advanced renal failure (calculated CrCl <15 mL/min); acute MI; 1,666 subjects screened; attending emergency physician's estimate of clinical probability of CHF recorded on a visual analog scale	Relative costs associated with false positives and false negatives computed for various BNP cut-points	BNP levels increased with increasing age; AUC by age 18-69 y: 0.915; 70-105 y: 0.844; AUC by sex male: 0.918 female: 0.870; Assumption that costs of false negatives outweighs costs of false positives leads to selection of relatively lower BNP cut points	Potential classification bias (by age and sex); hypothetical cost analysis	II
Maisel et al[16]	2003	Prospective, multicenter (7 sites in US and abroad); observational; N=1,538 (subjects who had clinical certainty of CHF determined by attending physician in the ED); N=452 (subjects who underwent ECHO within 30 days of ED visit)	Inclusion: ED patients with primary complaint of dyspnea; Exclusion: "overt cause of dyspnea"; advanced renal failure (calculated CrCl <15 mL/min); acute MI; 1,666 subjects screened; attending emergency physician's estimate of clinical probability of CHF recorded on a visual analog scale	Ejection fraction >45% defined as nonsystolic CHF	Subjects with nonsystolic CHF had lower mean BNP levels than subjects with systolic CHF (413 pg/mL vs 821 pg/mL); for distinguishing nonsystolic CHF from systolic CHF AUC=0.66	Selection bias (in terms of which subjects had ECHO performed)	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
McCullough et al[17]	2003	Prospective, multicenter (7 sites in US and abroad), observational; N=1,538 (subjects who had clinical certainty of CHF determined by attending physician in the ED); N=417 (subjects with history of asthma/COPD and no history of CHF)	Inclusion: ED patients with primary complaint of dyspnea; Exclusion: "overt cause of dyspnea"; advanced renal failure (calculated CrCl <15 mL/min); acute MI; 1,666 subjects screened; attending emergency physician's estimate of clinical probability of CHF recorded on a visual analog scale	Ejection fraction >45% defined as nonsystolic CHF	87 subjects (21%) had final adjudicated diagnosis of CHF; emergency physicians identified a minority of these cases (32/87); Cut point 100 pg/mL sensitivity 0.93 specificity 0.77	Post hoc analysis; concern that "criterion-standard" diagnosis may, in fact, not be more accurate as emergency physician diagnosis	II
McCullough et al[18]	2003	Prospective, multicenter (7 sites in US and abroad), observational; N=1,538 (subjects who had clinical certainty of CHF determined by attending physician in the ED); N=1,452 (subjects who had estimated GFR available)	Inclusion: ED patients with primary complaint of dyspnea; Exclusion: "overt cause of dyspnea"; advanced renal failure (calculated CrCl <15 mL/min); acute MI; 1,666 subjects screened; attending emergency physician's estimate of clinical probability of CHF recorded on a visual analog scale	Ejection fraction >45% defined as nonsystolic CHF	CHF more prevalent among subjects with advanced kidney disease; underlying kidney disease influences the "optimal" cut point for BNP; GFR >90 cut point: 71 pg/mL AUC: 0.91; GFR 60-89 cut point: 104 pg/mL AUC: 0.90; GFR 30-59 cut point: 201 pg/mL AUC: 0.81; GFR <30 cut point: 225 pg/mL AUC: 0.86	Post hoc analysis; potential classification bias (in setting of more advanced renal disease, more likely to diagnose CHF)	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
McCord et al[19]	2004	Prospective, multicenter (7 sites in US and abroad), observational; N=1,538 (subjects who had clinical certainty of CHF determined by attending physician in the ED); N=1,369 (subjects with recorded height and weight)	Inclusion: ED patients with primary complaint of dyspnea; Exclusion: "overt cause of dyspnea"; advanced renal failure (calculated CrCl <15 mL/min); acute MI; 1,666 subjects screened; attending emergency physician's estimate of clinical probability of CHF recorded on a visual analog scale	Conventional and lean BMI derived from actual or self-reported heights and weights	In patients with and without CHF, BNP levels are inversely correlated with BMI; AUC by BMI BMI <20: 0.90 BMI 20-24.9: 0.92 BMI >25: 0.89	Self-reports; potential misclassification bias (harder to ascertain cause of dyspnea in context of obesity)	III
Januzzi et al[20]	2005	Prospective, single-center, observational; N=600	Inclusion: ED patients with complaint of dyspnea; age ≥21; Exclusion: severe renal insufficiency (Cr >2.5 mg/dL); trauma; severe coronary ischemia (ST-segment elevation/depression >0.1 mV at presentation); >2 h delay after IV diuretic; unblinded NP measurement; NT-proBNP measurement: Elecsys 2010 (Roche); attending emergency physician's estimate of likelihood of CHF recorded on scale from 0% to 100%	Final diagnosis made by "study cardiologists" blinded to NT-proBNP results at 60-day review; if "unclear," or "in doubt" or "disagreement," adjudicated in accordance with Framingham criteria; (1) acute CHF (2) noncardiac dyspnea in patient with previous CHF (3) no CHF; for binary analyses, groups (2) and (3) combined	Final diagnoses: (1) 209 (35%) (2) 35 (6%) (3) 355 (59%); Cut point 300 pg/mL sensitivity 0.99 specificity 0.68; Cut point 450 pg/mL sensitivity 0.98 specificity 0.76; Cut point 600 pg/mL sensitivity 0.96 specificity 0.81; Cut point 900 pg/mL sensitivity 0.90 specificity 0.85; Cut point 1,000 pg/mL sensitivity 0.87 specificity 0.86; AUC clinical judgment 0.90 NT-proBNP 0.94 combined 0.96; Age influences "optimal" cut point; Age <50 (n=144) cut point: 450 AUC: 0.98; Age ≥50 (n=455) cut point: 900 AUC: 0.93	Convenience sample; excluded subjects with unblinded NP measurements, potential for spectrum bias; relatively low incidence of heart failure; concern that "criterion-standard" diagnosis may, in fact, not be more accurate as emergency physician diagnosis; potential for classification bias (by age)	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Krauser et al[21]	2005	Prospective, single-center, observational, N=204 (subjects with acute CHF and covariate data available)	Inclusion: ED patients with complaint of dyspnea; age ≥21 y; Exclusion: severe renal insufficiency (Cr >2.5 mg/dL); trauma; severe coronary ischemia (ST-segment elevation/depression >0.1 mV at presentation); >2 h delay after IV diuretic; unblinded NP measurement; NT-proBNP measurement: Elecsys 2010 (Roche); attending emergency physician's estimate of likelihood of CHF recorded on scale from 0% to 100%; (not clear how height and weight data were gathered); BNP measurement: ADVIA Centaur (Bayer)	Final diagnosis made by "study cardiologists" blinded to NT-proBNP results at 60-day review; if "unclear," or "in doubt" or "disagreement," adjudicated in accordance with Framingham criteria; (1) acute CHF (2) noncardiac dyspnea in patient with previous CHF (3) no CHF; for binary analyses, groups (2) and (3) combined; BMI categorized as normal, overweight, or obese using WHO/NIH classification scheme	Normal: 81 Overweight: 59 Obese: 64; BNP and NT-proBNP decrease with increasing BMI; among overweight/obese patients, sensitivity of BNP and NT-proBNP reduced using standard cut points; BNP (100 pg/mL) sensitivity: 0.80; NT-proBNP (900 pg/mL) sensitivity: 0.87	Specificity of NPs in overweight patients not addressed; potential misclassification bias (harder to ascertain cause of dyspnea in context of obesity)	III
Ray et al[22]	2004	Prospective, single-center, observational; substudy of EPIDASA (epidemiologic study of acute dyspnea in elderly patients); N=380	Inclusion: presentation to ED with acute dyspnea of <2 weeks as the prominent complaint; age >65 y; *plus 1 or more of the following*: respiratory rate >25; $Pa0_2$ <70 mm Hg; PaCO2 >45 mm HG with pH <7.25; $Sp0_2$ <92%; Exclusion: none; BNP measurement: triage (Biosite)	Final diagnosis determined by 2 independent experts (pulmonologist, cardiologist, internist, geriatrician, emergency physician), blinded to BNP data; in case of disagreement, consensus reached by third expert; isolated right heart failure considered as no cardiogenic pulmonary edema	Final diagnosis: cardiogenic pulmonary edema: 141 no cardiogenic pulmonary edema: 167; Cut point 100 pg/mL sensitivity 0.90 specificity 0.59; Cut point 150 pg/mL sensitivity 0.85 specificity 0.71; Cut point 200 pg/mL sensitivity 0.82 specificity 0.84; Cut point 250 pg/mL sensitivity 0.78 specificity 0.90; AUC=0.87	Convenience sample; limited to subjects with severe dyspnea	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Davis et al[23]	1994	Prospective, single-center observational; N=52	Inclusion: subjects requiring urgent admission for acute dyspnea; Exclusion: "obvious" pneumonia, pulmonary thromboembolism, pneumothorax; severe renal failure; acute chest pain; atrial natriuretic peptide and BNP measurement: locally developed immunoassays	Cause of dyspnea assessed retrospectively by "committee of physicians and a radiologist"; (1) primary lung disease without evidence of heart failure, (2) heart failure alone, (3) heart failure with underlying primary lung disease; cor pulmonale not considered heart failure	Final diagnoses: (1) 20 subjects; (2) 12 subjects; (3) 20 subjects Cut point 76 pg/mL sensitivity 0.93 specificity 0.90	Small sample size; vague inclusion and exclusion criteria	III
Fleischer et al[24]	1997	Prospective, single-center observational; N=123	Inclusion: subjects requiring admission for worsening dyspnea of any cause; BNP measurement: locally developed immunoassay	"Intent to treat" as determined by chart review; final diagnosis determined by member of study group (? blinded)	Final diagnoses: heart failure 22; primary lung disorder 80; pneumonia 20	Small sample size; low incidence of heart failure; lack of blinding?	III
Dao et al[25]	2001	Prospective, single-center observational; N=250 (June – October 1999)	Inclusion: patients presenting to urgent-care/ED with SOB as prominent complaint; Exclusion: dyspnea "clearly not secondary to CHF"; ACS, unless "predominant presentation was CHF"; BNP measurement: triage (Biosite)	Independent review by 2 cardiologists blinded to BNP levels and emergency physician's diagnosis (1) dyspnea due to CHF (2) baseline LV dysfunction without HF exacerbation (3) dyspnea not due to CHF	Final diagnoses: (1) 97 (39%); (2) 14 (6%); (3) 139 (55%) Cut point 80 pg/mL sensitivity 0.98 specificity 0.92 AUC Clinical judgment 0.88 BNP 0.98	Convenience sample (approximately 57% of eligible subjects enrolled); VA population (95% male); potential variability in application of exclusion criteria	III
Villacorta et al[26]	2002	Prospective, single-center, observational; N=77	Inclusion: consecutive ED patients with acute dyspnea; Exclusion: patients with a "clear diagnosis" (eg, tracheal stenosis, cardiac tamponade); patients with ACS whose prominent complaint was not dyspnea BNP measurement: triage (Biosite)	Cardiologist assigned definitive diagnosis, blinded to BNP measurements	Cut point 200 pg/mL sensitivity 100% specificity 97% AUC=0.99	Small sample size; vague inclusion and exclusion criteria; single reviewer	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Mueller et al[27]	2004	Single-center, prospective, randomized, controlled; N=452	Inclusion: consecutive adults presenting to ED with severe dyspnea as primary symptom; Exclusion: severe renal disease (Cr >2.8 mg/dL); cardiogenic shock; Subjects randomized to rapid bedside BNP measurement vs standard clinical evaluation; BNP measurement: triage (Biosite); Protocol used 100 pg/mL and 500 pg/mL as suggested cutoffs	Primary: Time to discharge; treatment cost; Secondary: Inhospital and 30-day mortality	Reduced need for hospitalization (75% vs 85%); Reduced need for ICU admission (15% vs 24%); Reduced median time to discharge (8 days vs 11 days); Reduced mean cost of treatment ($5,410 vs $7,264); 30-day mortality (10% vs 12%)	COPD more likely to be diagnosed in the BNP measurement group; one third of cost savings as a result of alternative diagnosis, consistent with high negative predictive value of low BNP level; single center	I
Mueller et al[28]	2004	Single-center, prospective, randomized, controlled; N=190 (women subjects)	Inclusion: consecutive adults presenting to ED with severe dyspnea as primary symptom; Exclusion: severe renal disease (Cr >2.8 mg/dL); cardiogenic shock; Subjects randomized to rapid bedside BNP measurement vs standard clinical evaluation; BNP measurement: triage (Biosite); Protocol used 100 pg/mL and 500 pg/mL as suggested cutoffs	Primary: Time to discharge; treatment cost; Secondary: Inhospital and 30-day mortality	Reduced need for hospitalization (73% vs 86%); Reduced need for ICU admission (12% vs 23%); Reduced median time to discharge (6 days vs 10 days); Reduced mean cost of treatment ($4,781 vs $6,843)	COPD more likely to be diagnosed in the BNP measurement group; one third of cost savings as a result of alternative diagnosis, consistent with high negative predictive value of low BNP level; single center	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Mueller et al[29]	2005	Single-center, prospective, randomized, controlled; N=240 (subjects with kidney disease)	As above, but limited to subjects with calculated GFR <60 mL/min	As above	Subjects with kidney disease older, more likely to have CHF as cause of acute dyspnea, higher rates of admission, inhospital and 30-day mortality; BNP testing had no impact on time to discharge and total cost of treatment in subgroup of patients with kidney disease	Post hoc subgroup analysis; protocol did not have separate cutoffs for subjects with kidney disease; smaller sample size, underpowered to detect small benefit?	II
Bayes-Genis et al[30]	2004	Prospective, single-center, observational; N=89	Inclusion: consecutive ED patients with acute dyspnea; shortness of breath at rest as "most prominent complaint"; Exclusion: NYHA classes I and II; age <40; chest trauma; cardiac tamponade; ACS, unless predominant symptom was heart failure; "severe" renal insufficiency; liver cirrhosis; NT-proBNP measurement: Elecsys 2010 (Roche)	Final diagnosis determined by 2 cardiologists blinded to NT-pro-BNP levels; (1) decompensated heart failure; (2) "masked heart failure," RV or LV dysfunction in the presence of pulmonary disease, producing overlapping signs and symptoms; (3) noncardiac dyspnea; For binary analyses, groups (1) and (2) combined	Final diagnoses: (1) 52; (2) 22; (3) 15 Cut point 254 pg/mL sensitivity 0.99 specificity 0.47 Cut point 423 pg/mL sensitivity 0.96 specificity 0.60 Cut point 593 pg/mL sensitivity 0.94 specificity 0.73 Cut point 762 pg/mL sensitivity 0.91 specificity 0.73 Cut point 973 pg/mL sensitivity 0.91 specificity 0.93 Cut point 1,100 pg/mL sensitivity 0.90 specificity 0.93 AUC=0.96	Ambiguous exclusion criteria; unusual classification of final diagnoses (counting any patients with RV or LV dysfunction as having "cardiac" dyspnea)	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Alibay et al[31]	2005	Prospective, single-center, observational; N=160	Inclusion: patients referred to ED with "acute dyspnea"; BNP measurement: triage (Biosite); NT-proBNP measurement: Elecsys 2010 (Roche)	Diagnosis of CHF made by 2 senior cardiologists	Final diagnoses: CHF: 60; Non-CHF: 100 BNP Cut point 50 pg/mL sensitivity 0.99 specificity 0.31 Cut point 100 pg/mL sensitivity 0.98 specificity 0.47 Cut point 150 pg/mL sensitivity 0.94 specificity 0.61 Cut point 200 pg/mL sensitivity 0.87 specificity 0.64 AUC=0.82 NT-proBNP Cut point 280 pg/mL sensitivity 1.00 specificity 0.05 Cut point 600 pg/mL sensitivity 1.00 specificity 0.51 Cut point 1,000 pg/mL sensitivity 0.97 specificity 0.63 Cut point 1,250 pg/mL sensitivity 0.87 specificity 0.66 AUC=0.84 BNP and NT-proBNP highly correlated (r=0.85)	Convenience sample; vague inclusion criteria; lack of blinding?	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Mueller et al[32]	2005	Prospective, single-center, observational; N=251	Inclusion: consecutive ED patients with shortness of breath as a chief complaint; Exclusion: STEMI, NSTEMI/ACS, trauma; BNP measurement: AxSYM (Abbot); NT-proBNP measurement: Elecsys 2010 (Roche)	Final diagnosis determined by single reviewer, blinded to NP data, using explicit criteria; Subjects without reference standard for diagnosis (n=11) or with "inconclusive" diagnosis (n=9) excluded from analysis	Final diagnosis: CHF: 137; Non-CHF: 114 BNP Cut point 100 pg/mL sensitivity 0.96 specificity 0.61; Cut point 118 pg/mL sensitivity 0.95 specificity 0.64; Cut point 160 pg/mL sensitivity 0.90 specificity 0.73; Cut point 295 pg/mL sensitivity 0.80 specificity 0.86; AUC=0.92; NT-proBNP Cut point 292 pg/mL sensitivity 0.95 specificity 0.53; Cut point 125 pg/mL (age <75), 450 pg/mL (age ≥75)* sensitivity 0.94 specificity 0.46; Cut point 476 pg/mL sensitivity 0.90 specificity 0.65; Cut point 825 pg/mL sensitivity 0.87 specificity 0.81; *manufacturer-recommended age-stratified cut points AUC=0.90; Age and renal function had no impact on diagnostic utility of either test	Stringent study design; explicit criteria for CHF may have missed cases of isolated diastolic dysfunction; overwhelming predominance of men (93%)	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Ray et al[33]	2005	Prospective, single-center, observational; substudy of EPIDASA (epidemiologic study of acute dyspnea in elderly patients); N=202	Inclusion: presentation to ED with acute dyspnea of <2 weeks as the prominent complaint; age >65 y; *plus 1 or more of the following*: respiratory rate >25; $Pa0_2$ <70 mm Hg; PaCO2 >45 mm HG with pH <7.25; $Sp0_2$ <92%; Exclusion: none; BNP measurement: triage (Biosite); NT-proBNP measurement: Elecsys 2010 (Roche)	Final diagnosis determined by 2 independent experts (pulmonologist, cardiologist, internist, geriatrician, emergency physician), blinded to BNP data; in case of disagreement, consensus reached by third expert	Final diagnosis: cardiogenic pulmonary edema: 88; no cardiogenic pulmonary edema: 114; BNP "optimal" cut point: 250 pg/mL; sensitivity 0.73 specificity 0.91; AUC=0.85; NT-proBNP "optimal" cut point: 1,500 pg/mL; sensitivity 0.75; specificity 0.76; AUC=0.80; BNP and NT-proBNP highly correlated (r=0.91)	Limited to subjects with severe dyspnea; overlapping population with Ray 2004?	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Lainchbury et al[34]	2003	Prospective, single-center, observational; N=205	Inclusion: dyspnea as "part of the reason for presentation" to the ED; BNP measurement: locally developed immunoassay; triage (Biosite); NT-proBNP measurement: locally developed immunoassay; Elecsys 2010 (Roche)	Final diagnosis made by 2 independent cardiologists blinded to BNP/NT-proBNP results; in cases of disagreement a third cardiologist was the final adjudicator; "All patients with heart failure fulfilled the Framingham CHF score criteria"	Final diagnosis: heart failure: 70; non–heart failure: 135; Biosite BNP Cut point 69 pg/mL sensitivity 0.97 specificity 0.44; Cut point 104 pg/mL sensitivity 0.97 specificity 0.49; Cut point 208 pg/mL sensitivity 0.94 specificity 0.70; Cut point 277 pg/mL sensitivity 0.83 specificity 0.78; Cut point 346 pg/mL sensitivity 0.77 specificity 0.84; AUC=0.89; Roche NT-proBNP Cut point 140 pg/mL sensitivity 0.87 specificity 0.71; Cut point 240 pg/mL sensitivity 0.83 specificity 0.82; Cut point 340 pg/mL sensitivity 0.80 specificity 0.87; Cut point 440 pg/mL sensitivity 0.74 specificity 0.90; Cut point 540 pg/mL sensitivity 0.68 specificity 0.92; AUC=0.89	Convenience sample; vague inclusion criteria	II
Rasanen et al[36]	1985	Prospective randomized controlled trial; N=40	Inclusion: Acute pulmonary edema with chest x-ray findings; Interventions: Mask CPAP 10 vs mask and ambient pressure FiO_2=28–30% → if treatment failure then routine care per physician	1°: Intubation rate, outcome after discharge, pH, PaO_2, CO_2; Treatment failure if after 10 min of treatment: PO_2 <50, pCO2 >55 or respiratory rate >35	CPAP significantly improved pH, PO_2, respiratory rate, heart rate, BP; no significant reduction in intubation or mortality Mortality CPAP=3/20; control=6/20 +15% difference	Small sample; consecutive?; FiO_2 low and not varied for individual; good randomization with similar disease in each group	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Lin and Chiang[37]	1991	Prospective randomized controlled trial; N=80	Inclusion: impending respiratory failure (respiratory rate >22, PO_2/FiO_2 >200, $AaDO_2$ >200), pulmonary edema clinically and on chest radiograph of cardiac origin; Interventions: all 80 patients received Swan-Ganz catheter and arterial line for ABG and blood pressure; all 80 patients received FiO_2=1 by face mask for 30 min; then, N=40 randomly chosen to receive serial CPAP therapy (cm H_2O = 2.5, 5, 7.5, 10, 12.5) for 30 min intervals x 5 (total 3 h) vs N=40 control of FiO_2=1 by face mask; measurements taken at the end of each 30 min period prior to change; after 3 h, CPAP and FiO_2 adjusted to keep PaO_2 ≥ 80; measurements repeated every 30 min for 3 more h; 10 patients excluded from control group and 15 patients excluded from CPAP group	Primary: need for endotracheal intubation (therapeutic failure rate after 6 h); Secondary: systemic arterial pressure, PAP, PCWP, cardiac output	Results: only N=20 in each group completed the first 3 h period; N=5 in the CPAP arm and N=10 in the control O_2 arm were treatment failures (not statistically significant); by 6 h, N=18 patients left in the CPAP arm and N=12 left in the control group; N=7 total CPAP patients of 25 and N=18 of the control arm were therapeutic failures; statistically less need for intubation in the CPAP group (N=7 vs N=17 in O_2 arm), no difference in 24 h mortality; statistically greater reduction in BP, heart rate, and rate pressure product in CPAP vs O_2 alone arm; PO_2, $AaDO_2$, and intrapulmonary shunt was statistically better in CPAP group vs O_2 alone arm; otherwise, no statistical difference in hemodynamics or $PaCO_2$; Mortality: CPAP=2/40; control=4/40 +5% difference	Limitations: ICU patients, chosen and treatment assignment "random" without description of process, no description of differences in medical therapy; no description of how chose the CPAP pressure	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Bersten et al[38]	1991	Prospective randomized controlled trial; N=39; planned=40	Inclusion: pulmonary edema PO_2 <70 or CO2 >45 on O_2 8 lpm mask; Interventions: mask CPAP 10 vs conventional O_2 control (FiO_2 60-100 for SO_2 ≥95)	1°: Intubation rate, 2°: BP, respiratory rate, heart rate, ABG, lactate, CK-MB, electrolytes	CPAP significantly reduced intubation, respiratory rate, pCO_2, increasing pH and PO_2/FiO_2 vs control; Mortality (ICU) CPAP=2/19 control=4/20 +9.5% difference	Small sample; consecutive?; good randomization as evident by similar illness; do not describe where O_2 measures taken on devices	I
Baratz et al[39]	1992	Prospective self-controlled ICU study; N=13	Inclusion: signs of severe CHF (dyspnea, orthopnea, elevated JVP, ventricular gallop, PCWP >20); awake, alert, and able to assist in their care, no evidence of dysrhythmia or ischemia; Interventions: nasal CPAP 5, 10, and 15 cm water for 20 min each within 24 h of Swan-Ganz and at least 4 h after last diuretic; baseline mask breathing measures and CPAP withdraw measures also recorded; treatment stopped if: systolic blood pressure <100, respiratory rate >35, cardiac output decrease by 15% from baseline, or unable to wear mask; O_2 to keep SO_2 >90%	Primary: "response"= cardiac output increase ≥400 mL Secondary: respiratory rate, heart rate, BP, PAP, ABG, mixed venous blood gas, LVEF by nuclear scintigraphy or echo	Results: N=7/13 responded and N=6 nonresponders to CPAP; responders had significantly increased cardiac output, cardiac index, stroke volume, stroke volume index, oxygen uptake (VO_2) and oxygen delivery DO_2 vs baseline; improvements were lost after CPAP withdrawal	Limitations: small study, more medical therapy in CPAP responders, ICU patients well enough to wait hours, no description of which pressure is best	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Lin et al[40]	1995	Prospective randomized controlled trial; N=100	Inclusion: acute cardiopulmonary edema sent to CCU; Interventions: increasing face mask CPAP vs high FiO_2 O_2	Primary: therapeutic failure; Secondary: intubation, cardiopulmonary measures	CPAP significantly better than O_2 alone at decreasing heart rate, decreasing systolic BP, decreasing rate pressure product, decreasing intrapulmonary shunt, decreasing A-a gradient, and increasing stroke volume; PaO_2 increased significantly with increased CPAP pressures; less treatment failure in CPAP 12 (24%) vs O_2 alone 25 (50%); both CPAP and O_2 alone reduced PCWP, mean CVP; no differences in length of stay or mortality; Mortality (inhospital) CPAP=4/50 control=4/50 Mortality (1 y) CPAP=12/50 control=14/50 Overall difference in both groups is +4%	CCU patients primarily from ED; consecutive?; larger sample of trials; did not show all results in tables but described them	II
Lenique et al[41]	1997	Prospective, self-controlled, non-randomized; N=9	Inclusion: admitted to CCU with clinical signs of severe CHF (dyspnea, orthopnea, increased JVP, S3 heart sound, PAOP ≥18 with cardiac index <2.8); no patients were unstable, had arrhythmia, or had acute MI; Interventions: ≥6 h after last diuretic and ≥1 h after last dilator or inotrope; face CPAP (0 → 5 → 10→ 0) and O_2 FiO_2=35%; Exclusion: febrile, sepsis, pneumonia, altered mental status, or risk of aspiration	Measures: cardiopulmonary measures including Swan	Results: PaO_2 significantly increased at CPAP 10; respiratory rate and PCO_2 did not significantly change; work of breathing significantly decreased at CPAP 10; no change in heart rate; pulmonary artery occlusion pressures and right atrial pressures significantly decreased at CPAP 10; CPAP 10 significantly increased lung elasticity and decreased resistance; no significant change in stroke volume index	Limitations: Swan measurements while supine (? ethical); small sample; CCU patients; Strengths: good discussion of cardiopulmonary parameters	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Kelly et al[42]	1997	Retrospective case series; N=75	Inclusion: history and physical examination consistent with acute pulmonary edema, chest radiograph confirmation, PaO_2 <60, SO_2 <90 or <93% on FiO_2 8 lpm O_2 by mask; did not exclude patients with history of COPD; Intervention: face mask CPAP; Exclusion: cardiogenic shock, intubated before arrival	Age, use of CPAP, complications, admission disposition, intubation, length of stay, mortality in ED and inhospital	3 (4%) intubated (all with acute MI by CK), 5 (7%) failed to tolerate mask, 2 (3%) hypotensive ≤80, 3 (4%) cardiac dysrhythmia (brady, ventricular tachycardia, asystole), 67 (89%) without adverse events; average duration of CPAP 1.9 (0.25-7.5 range) h; inhospital mortality 11 (15%) CPAP vs 4 (13%) not treated with CPAP (*NOTE: these numbers mean that most patients were treated with CPAP); average length of stay=8 days; 71% general ward and 13 (17%) CCU, 4 (5%) ICU, 4 (5%) transferred to other hospitals	Limitations: case series, selection bias: CPAP indication not predetermined; general physician assessment, small sample; use of CPAP at discretion of physician, therefore unable to compare CPAP and no CPAP	III
Takeda et al[43]	1998	Prospective randomized controlled trial; N=29 MI patients with pulmonary edema	Inclusion: MI and pulmonary edema with respiratory distress and PO_2 <80 on FiO_2 50%; Interventions: Intubated vs nasal CPAP 4-10 vs conventional O_2	Intubation, hemodynamics, respiratory rate, ABG, in-house mortality, endothelin	CPAP vs control group significantly reduced intubation, inhospital mortality, heart rate, 24 h PCWP, magnitude of respiratory rate reduction (respiratory rate decreased significantly in both but more in CPAP), 24 h endothelin, and increased 24 h PO_2/FiO_2; Mortality CPAP=1/11 control=7/11 55% difference	Consecutive patients; small sample size; no power to comment on mortality; slightly more use of inotropes in control (?) sicker	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
L'Her et al[44]	2004	Prospective randomized controlled trial; N=89	Inclusion: age ≥75, acute respiratory failure due to cardiopulmonary edema (PaO_2/FiO_2 ≤300 with oxygen 8 lpm for 15 min, respiratory rate ≥25, access respiratory muscle; Interventions: face mask CPAP 7.5 vs standard mask O_2; both medical treatment	Primary: 48-h mortality; Secondary: respiratory and hemodynamics, intubation, complications, length of stay, and inhospital mortality	Study suspended after interim analysis; CPAP less 48 h mortality and less complications vs standard treatment; CPAP also reduced heart rate and respiratory rate more than standard treatment; significantly less need for mechanical ventilation in CPAP; no difference in length of stay; no difference in development of hypercapnea; Baseline to 1 h → CPAP significant reduction in respiratory rate and increase in PaO_2/FiO_2; no difference among standard treatment; not large enough sample to study long-term all-cause mortality	Limitations: unblinded treatment, crossover may have influenced mortality (ie, made less of a difference); Strengths: consecutive patients; relatively well-designed study that controlled for many variables; similar disease characteristics at baseline between treatments	I
Pang et al[45]	1998	Meta-analysis of Rasanen et al,[36] Bersten et al,[38] and Lin et al[40] studies	Inclusion: patients presenting to a hospital with acute pulmonary edema; Analysis: randomized studies of CPAP vs control, NPPV vs control, or CPAP vs NPPV	Hospital survival, need for endotracheal intubation, predischarge left ventricular dysfunction	CPAP vs control (3 studies): insignificant trend to improved mortality; significantly less endotracheal intubation NNT=4 to prevent 1 intubation; LV function (1 study, Lin et al) found no difference; NPPV vs control (none); CPAP vs NPPV (1 study, Bersten et al): no difference in inhospital mortality, or rate of intubation; no data about LV dysfunction	Few studies available for analysis; individual study weaknesses as previously noted in individual study grading; variable degrees of study homogeneity related to different outcome measures	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Kelly et al[46]	2002	Prospective randomized controlled trial; N=58	Inclusion: acute breathlessness (<6 h), respiratory rate >20, bibasilar rales, chest radiograph showing pulmonary edema; Interventions: face mask CPAP 7.5 with O_2 (N=27) vs O_2 via venturi mask (N=31); both FiO_2=60%; minimum treatment 6 h or until no longer needed; Exclusion: chest radiograph: pneumonia/pneumothorax; out–of–hospital treatment other than O_2/diuretics/opiates	Heart rate, respiratory rate, BP, SO_2, plasma epinephrine, norepinephrine, and BNP levels at 0, 1, 6, 24 h; ABG at 0 and 1 h; echocardiogram to assess LV function; visual analogue score of dyspnea 1 and 6 h after treatment	CPAP significantly less breathlessness at 1 h; significantly more improvement in respiratory rate, heart rate, and acidosis; no significant difference in length of stay or mortality but trended better in CPAP; (not powered); no significant difference in plasma neurohumoral concentrations; Mortality CPAP=2/27 control=7/31 +16.1% difference	Limitations: small study; limited *P* values listed; baseline CK higher in O_2 alone group and PO_2 higher in CPAP group (? significance); no clear calculations of *P* value; less specific methods; no clear primary or secondary outcome measures; Strengths: consecutive patients	II
Newberry et al[48]	1995	Case reports (2); N=2	Inclusion: patient who would otherwise have required endotracheal intubation; ? no criteria; Interventions: 2 case reports: nasal mask BiPAP 10/5 and BiPAP 8/3	Primary: ABG results, dyspnea, and clinical improvement	Results: both patients experienced improvements in pH, PCO_2, PO_2, SO_2, dyspnea; ? significant	Limitations: 2-person case report; small number; no statistically significant calculations (expected, given case reports); 1 patient had end-stage renal disease and otherwise normal heart	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Rusterholtz et al[51]	1999	Prospective, uncontrolled case series; N=26	Inclusion: 26 consecutive patients with severe pulmonary edema in ICU; Interventions: face mask NIPSV 20/3.5 adjusted for tidal volume=7-10 mL/kg; FiO_2 100% → ↓ if SO_2 >95%	Primary: intubation Secondary: respiratory rate, SO_2, heart rate, mean arterial pressure, Glasgow Coma Scale Score, respiratory muscle workload, ECG, chest radiograph, ABG, electrolytes, CK-MB, liver function test, illness severity score, blood cell count	5 (21%) failures and 21 (79%) successes; NIPSV significantly decreased respiratory rate, decreased mean arterial pressure, increased SO_2, decreased PCO_2, increased PO_2, increased pH; low PCO_2 was predictive of BiPAP failure; 80% of treatment failure patients died of MI vs 2/21 in treatment success group; significantly more MI in treatment failure group (4 of 5, 80%) than success (2 of 21, 10%); do not use BiPAP in low PCO_2 or MI	Small case series; uncontrolled	III
Mehta et al[52]	1997	Prospective, randomized controlled trial; N=27; planned=40; stopped early due to MI rate in BiPAP vs CPAP	Inclusion: university ED, with acute pulmonary edema and respiratory rate >30, heart rate >100; Interventions: nasal BiPAP 15/5 (N=14) vs nasal CPAP 10 (N=13) vs conventional O_2 (historical control); O_2 to keep SO_2 >90	1°: heart rate, respiratory rate, BP, SO_2, ABG, lactate, ECG, cardiac enzymes; 2°: intubation rate, time ventilated, ICU stay, hospital length of stay, mortality	MI: 11 BiPAP vs 4 CPAP (P=0.02); 38% control, 71% BiPAP, 31% CPAP (P=0.05); dyspnea, pCO_2, respiratory rate, heart rate, pH, BP significantly lowered at 30 min in BiPAP, not CPAP; no difference in 2° outcomes; Mortality CPAP=2/13 BiPAP=1/14; difference of –1%	Many MIs in BiPAP, which likely existed at presentation by rule in time, likely sicker group; quality of randomization?; consecutive?; small study, although stopped early	III
Masip et al[53]	2000	Prospective randomized controlled trial; N=37; planned=40	Inclusion: ED or ward with cardiogenic pulmonary edema; Interventions: face mask BiPAP (N=19) vs O_2 venturi mask (N=18) (control); Resolution=clinical improvement with respiratory rate <30 and O_2 ≥96%; BiPAP inspire; pressure adjusted to give >400 ml T; PEEP=5	1°: Intubation rate, and resolution time; 2°: heart rate, respiratory rate, BP, SO_2, ABG, lactate, cardiac enzymes	Intubation: 6 (33%) control vs 1 (5%) NIPSV; P=0.04; Resolution: (min): 30 (15-53) NIPSV vs 105 (50-230) control P=0.002	Small study; ? consecutive patients; control group was sicker; required greater "intensive" attention to ensure proper use; treatment in ICU	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Sharon et al[54]	2000	Randomized controlled trial; N=40	Inclusion: severe pulmonary edema with SO_2 <90 by pulse oximetry; Interventions: face mask BiPAP O_2 and conventional isosorbide dinitrate vs high dose isosorbide dinitrate bolus with conventional O_2; BiPAP=8/3 mm Hg	Primary: death, intubation, or MI within 24 h of admission; Secondary: speed of recovery (decrease in heart rate, respiratory rate, and increased SO_2)	Significantly more intubation 14 (80%) vs 4 (20%); MI within 24 h 11 (55%) vs 2 (10%); combined endpoint (death, intubation, MI) 17 (85%) vs 5 (25%) in Bi-PAP vs high dose nitro bolus group; significantly slower improvement by respiratory rate, heart rate, SO_2 in BiPAP vs high dose isosorbide dinitrate; SO_2 significantly improved in high dose isosorbide dinitrate vs BiPAP	Out–of–hospital study; consecutive patients; similar baseline characteristics; stopped at interim analysis due to worse outcome in BiPAP; did not address mild to moderate pulmonary edema; due to high-dose nitroglycerin or BIPAP?	III
Levitt[55]	2001	Prospective randomized controlled trial; not consecutive; convenience sample; N=38	Inclusion: severe respiratory distress and suspected CHF (respiratory rate ≥30, diaphoresis, access muscle use, rales, distended neck veins, peripheral edema, or a history of CHF); Interventions: nose or face mask BiPAP (8/3 but adjustable); ? FiO_2 (N=21) vs mask O_2 (N=17)+medical management	Primary: intubation within 24 h; Secondary: BP, heart rate, respiratory rate, SO_2, Borg dyspnea score, arterial pH, PO_2, pCO_2, acute MI incidence within 24 h	No significant difference in hospital length of stay, intubation, vital signs, pH or pCO_2, PO_2 BiPAP vs O_2; found Bersten et al's power analysis of 40 patients was possibly too small	Limitations: convenience sample; no known FiO_2 for BiPAP; more women in O_2 group, did not enroll enough patients for power analysis because realized would not have enough numbers given lower intubation rate than Mehta study; no definition of how randomized or chest pain/cardiac enzyme findings at presentation	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Chadda et al[56]	2002	Prospective crossover study; N=6	Inclusion: orthopnea, elevated JVP, S3 heart sound gallop, pulmonary arterial occlusion pressure of 18 mm or more, and cardiac index <2.8 $L*min^{-1}$ m^{-2}; Interventions: face mask CPAP 5, mask CPAP 10, face mask NIPSV 10/5 (5 pressure support and PEEP); >6 h after diuretic and >1 h after vasodilator or inotrope; O_2 to keep SO_2 >90%; Exclusion: sepsis, acute MI, arrhythmias	Measures: respiratory measures: esophageal pressure, dynamic pulmonary compliance, esophageal pressure time product; hemodynamic measures: heart rate, BP, intracardiac and transmural cardiac pressure, mPAP, mean right atrial pressure, cardiac output, stroke volume index, oxygen uptake	Only NIPSV statistically increased tidal volume and esophageal time product compared to spontaneous breathing; no significant difference in min ventilation, PaO_2, oxygen delivery, oxygen uptake, heart rate, BP, SV index; CPAP 10 and NPPV significantly reduced mean transmural right atrial pressure and mean transmural pulmonary artery occlusion pressure; NPPV causes a greater reduction in respiratory load vs CPAP 10 but without significant improvements in cardiac performance; CPAP 10 and NPPV almost significantly reduced cardiac output, which is bad; NPPV great for reducing work of breathing but no improvement in cardiac performance	Limitations: no report of constant FiO_2; very small numbers; Strengths: consecutive patients—why took so long?; invasive monitoring recording many hemodynamic variables	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Bellone et al[57]	2004	Prospective randomized controlled trial; N=46	Inclusion: ED patients with acute pulmonary edema (SO_2 <90 with >5 lpm O_2 by mask, moderate-to-severe dyspnea, respiratory rate >30, access muscles or paradoxical breathing with heart rate >100, gallops, bilateral rales, and chest radiograph indicating pulmonary edema without a history of aspiration or pneumonia); Interventions: face mask NIPSV 15/5 then IP adjusted to tidal volume=>400 (N=24) vs mask CPAP 10 (N=22); Exclusion: required immediate intubation, respiratory or cardiac arrest, ACS (typical chest pain, diagnosis ECG, or abnormal cardiac enzymes), hypotension <90, unresponsive, agitated, mask intolerant, normal chest radiograph, or chest radiograph with pneumonia	Outcome: Primary: incidence of acute MI; Secondary: intubation rate, gas exchange response to ventilatory treatment, and inhospital mortality	CPAP and NIPSV significantly improved pH, respiratory rate, and $PaCO_2$ after 1 h; PaO_2/FiO_2 did not improve after 1 h; no difference in acute MI (CPAP 13.6% vs NIPSV 8.3%) or intubation (CPAP 4.5% vs NIPSV 8.3%)	Limitations: sample size; excluded patients believed to have ACS at presentation, so cannot comment on these patients; perhaps pulmonary edema is a stress test that forbodes well future stresses such as NIPSV if patients not believed to have ACS at presentation; possible inadequate assumptions for power analysis; no statistical power to detect difference in MI; no control group of O_2 only; Strengths: well thought out with very strict definitions	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Cotter et al[58]	1998	Prospective, randomized, nonblinded clinical trial; 104 patients	Study patients had CHF and pulse oximetry <90%; group A received high-dose nitrates (ie, 3 mg IV isosorbide dinitrate every 5 min) and low-dose lasix (ie, 40 mg IV); group B received high-dose lasix (ie, 80 mg IV every 15 min) and low-dose nitrates (ie, 1 mg/hour IV isosorbide dinitrate); both groups received oxygen and morphine	Outcomes: need for mechanical ventilation within 12 h, death, MI, and cumulative endpoint	The high-dose nitrate and low-dose furosemide group had less frequent mechanical ventilation, MI, and a lower cumulative endpoint than the comparison group	Hypotensive patients excluded; treatment bias with every 15 min furosemide	II
VMAC Investigators[59]	2002	Prospective, randomized, double-blinded, placebo-controlled clinical trial; physicians decided which patients received heart catheterization; either nesiritide or nitroglycerin (randomly) added to control arms after 3 h; 489 patients	Either IV nitroglycerin, IV nesiritide, or neither given to decompensated heart failure patients in addition to "standard" therapy; placebo patients received either nitroglycerin or nesiritide after 3 h	PCWP in catheterized patients, hemodynamics, and patient self-reporting of dyspnea	2 mm Hg mean decease in PCWP for nesiritide compared to nitroglycerin (significant); both nesiritide and nitroglycerin associated with significantly greater reductions in pulmonary vascular resistance at 1 h compared to placebo; nitroglycerin significantly lowered mean right atrial pressure compared to placebo at 3 h; the nesiritide dyspnea scores at 3 h were significantly lower than placebo, although dyspnea scores for nesiritide and nitroglycerin were not significantly different from each other at 3 h	"Standard" care not standardized; decision to catheterize for PCWP made by physicians; alpha error exists for the PCWP outcomes; nitroglycerin probably underdosed (ie, 29-42 μg/min)	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Abraham et al[60]	2005	Retrospective analysis (prospectively entered) of observational patient data from ADHERE; patients who received nitroglycerin, nesiritide, milrinone, or dobutamine were reviewed	Not applicable	Odds ratios for inhospital mortality; risk factor and propensity score adjustments were made to the odds ratios; propensity scoring is a statistical technique that attempts to mitigate treatment bias	Mortalities for either nitroglycerin- or nesiritide-treated patients were lower than either dobutamine or milrinone; the unadjusted mortality odds ratio for nesiritide compared to nitroglycerin was 1.64 (95% CI 1.38-1.94); once adjusted for propensity scores and covariates, the mortality odds ratio for nesiritide compared to nitroglycerin decreased to 0.95 (95% CI 0.77-1.66)	Retrospective analysis of a database; clinical judgment guided use of intravenous medications, not study protocol; there was no nonintravenous vasoactive control group	II
Abraham et al[61]	1998	16 human subjects; prospective, randomized, double-blind, placebo-controlled, human study	Patients randomized to 3 groups: placebo and 2 escalating doses of nesiritide; measurements made over 4 h of treatment	Hemodynamic and neurohumoral outcomes	Nesiritide significantly decreased right atrial pressure, systemic vascular resistance, PCWP, and mean arterial pressure, and significantly increased cardiac index compared to baseline, whereas placebo did not	Small sample size; SVR decreased in placebo group compared to baseline (2,005-1,588 dynes.s.cm,$^{-5}$ P=0.06), and cardiac index increased in placebo group compared to baseline (1.58-2.01 L/min/m^2, P=0.06) suggesting treatment bias and beta error; 2 of 15 patients excluded from data analysis: hypotension (1 patient) and an apparent allergic reaction (1 patient)	III
Mills et al[62]	1999	103 subjects (NYHA class II-IV); multicenter, randomized, double-blind, placebo-controlled	3 escalating doses of (24 h infusions of) nesiritide	Central hemodynamics during 24-h infusions and 4 h after infusions	Nesiritide infusions decreased PCWP by 27%-39% within 6 h; 1 nesiritide dose significantly increased cardiac index compared to placebo	No significant limitations	I

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Colucci et al[63]	2000	432 subjects; multicenter trial; Arm 1: prospective, randomized, double-blind, placebo-controlled Arm 2: prospective, randomized, nonblinded, comparative trial	Arm 1: Nesiritide vs placebo for 6 h in right-heart-catheterized patients with decompensated heart failure; Arm 2: Nesiritide vs "standard therapy" over 7 days in patients with decompensated heart failure	Arm 1: Change in PCWP, global clinical status, dyspnea, and fatigue; Arm 2: Global clinical status, dyspnea, fatigue, and side effects	Arm 1: Low- and high-dose nesiritide decreased mean PCWPs by 6 mm Hg and 9.6 mm Hg, respectively; significantly reduced global clinical status, dyspnea, and fatigue; Arm 2: Global clinical status, dyspnea, and fatigue were similar for nesiritide and standard treatment arms	Inpatient management of decompensated heart failure; "standard treatment" for inpatients was not standardized in the second portion of the trial	III Arm I is Class II; Arm 2 is Class III
Burger et al[64]	2002	Prospective, randomized clinical trial	255 patients randomized to 1 of 3 arms: low-dose nesiritide, higher-dose nesiritide, and dobutamine	Hemodynamic measurements and 24-h Holter monitoring	Frequency of ventricular dysrhythmias and mean heart rate were higher in the dobutamine arm than the 2 nesiritide groups	Not blinded; no "placebo" control; selection bias: more Class IV CHF patients in dobutamine arm (36%) than either nesiritide arm (20% and 23%; P=0.04)	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Sackner-Bernstein et al[65]	2005	Meta-analysis of 5 prospective, randomized, clinical trials; 1,269 patients	Not applicable	Relative risk of increase in serum creatinine (nesiritide vs control) and frequency of the need for dialysis or medical intervention for renal insufficiency	Compared with non–inotrope-based control therapy (eg, diuretics and other vasodilators), nesiritide increased the risk of worsening renal function: nesiritide dose 0.03 μg/kg/min, relative risk 1.52, 95% CI 1.16-2.0; nesiritide dose 0.015 μg/kg/min, relative risk 1.46, 95% CI 1.09-1.95; for nesiritide delivered at any dose compared to control: relative risk 1.53, 95% CI 1.16-2.0; nesiritide patients were more likely to require medical intervention for renal issues: relative risk 2.29, 95% CI 1.07-4.89; the rate of medical interventions among nesiritide patients was 11.9%, vs controls at 4.2%; there was no significant difference between nesiritide and control in terms of the need for dialysis	No assessment of the quality or validity of the individual trials; no description of trial sites or participants to assess ability to combine data; not clear if data abstraction was duplicate or verified; tests for heterogeneity are low-powered	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Sackner-Bernstein et al[66]	2005	Pooled analysis of 3 prospective clinical trials (out of 12 originally identified) of nesiritide in acutely decompensated heart failure; data extracted from FDA documents, sponsor documents, and published peer review articles (862 subjects); articles included if 6-h nesiritide infusions used, control groups without vasopressors used, and 30-day mortality reported	Not applicable	30-day mortality	30-day mortality nesiritide: 35/485 (7.2%) control: 15/377 (4%); Risk ratio from meta-analysis: 1.74 (95% CI 0.97-3.12); Hazard ratio after adjusting for study: 1.80 (95% CI 0.98-3.31)	No description of trial sites to assess combinability, although participants are now described; not clear if data abstraction was duplicate, or verified, etc; 1 issue that is not clear is whether there was any adjustment for site clustering in the Cox models; the increased death rate is not significant after adjusting for risk factors, inotrope use, study, etc, so the appropriate conclusion is that greater mortality in the nesiritide group cannot be confidently excluded	I
Abraham[68]	2005	Retrospective review of prospectively collected database	Subjects treated with nitroglycerin, nesiritide, dobutamine, or milrinone	Inhospital mortality	Adjusted mortality odds ratio for nesiritide compared to nitroglycerin 0.94 (95% CI 0.77-1.66); nitroglycerin and nesiritide each outperformed dobutamine and milrinone	No randomization and potential selection and treatment bias; potential bias adjusted by authors using risk factor and propensity score-adjusted odds ratios	II
Verma et al[69]	1992	36 subjects; prospective, randomized, single-blind, nonplacebo-controlled trial	Subjects randomized to 3 arms: enalapril, isosorbide and nitroglycerin, and doxazosin	Central hemodynamic measurements	Enalapril significantly decreased PCWP (ie, 6-7 mm Hg mean decrease) compared to baseline within 90 min	Selection bias: all patients had clinical presentation and ECG consistent with MI or unstable angina; small sample size; single blinded	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Agusti et al[70]	2003	Meta-analysis of 51 publications analyzing ACE inhibitor use vs controls in decompensated heart failure patients	ACE inhibitor use in chronic decompensated heart failure patients	Adverse events from ACE inhibitor use in decompensated heart failure	Cough, hypotension, renal dysfunction, dizziness, hyperkalemia, and impotence significantly more likely to occur in ACE patients vs control	Chronic decompensated heart failure patients, not acute management; data obtained "from the authors" in 29 of 51 trials because missing from the publications	II
Anthopoulos et al[71]	2001	Prospective, randomized, clinical trial	240 patients with CHF randomized to 1 dose of either captopril or perindopril; continuous hemodynamic measurements made after the first dose	Hemodynamic measurements (eg, BP, pulse)	Captopril significantly lowered BP in the first 2 h after the first dose compared to perindopril	No control group; not blinded; not emergency patients	III
McElnay et al[72]	1996	6 subjects; prospective, randomized, single-blind, crossover study	Each patient received 12.5 mg of sublingual captopril; after a 1-week washout period, the same procedure was followed for a single oral dose of captopril	Serial hemodynamic and serum concentration measurements	Sublingually, the peak serum captopril level occurred at a median of 40 min; orally, the median peak serum concentration occurred at 90 min (significant); blood pressure dropped earlier in the sublingual group	Small sample size	III
Podbregar et al[73]	1999	20 subjects; prospective, randomized, nonblinded, nonplacebo-controlled comparison of 2 treatment methods	10 subjects received an enalaprat IV bolus, and 10 subjects received a 1-h continuous infusion of the same amount of medication	Hemodynamic measurements	Both administration methods significantly lowered mean pulmonary artery pressures by at least 20% (ie, 6 mm Hg) compared to baseline; both methods also significantly lowered mean arterial pressure compared to baseline	Small sample size; indirect outcomes	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Vitovec et al[74]	2000	298 patients; multicenter, prospective, single-blind, randomized, nonplacebo-controlled comparison of 2 treatment regimens; NYHA Class II-IV patients	Patients randomized to a single oral dose of 2.5 mg of enalapril or 2.0 mg of perindopril	Serial hemodynamic measurements	Significant drop in systolic and diastolic blood pressures (compared to baseline) for enalapril 4 h after ingestion; more than 20 mm Hg drop in systolic blood pressure occurred in 31 enalapril patients; no significant difference between treatment arms	No placebo arm; single blinded	II
Francis et al[75]	1985	Treatment; nonrandom; N=15	Clinically stable advanced heart failure patients; Swan-Ganz catheter monitoring pre/postlasix 1.3 mg/kg IVP	Hemodynamics by Swan-Ganz catheter and urine output	IV lasix dose resulted in transient (1-2 h) worsening, with increased heart rate, mean arterial pressure, LV filling pressure, and decreased stroke volume	Physiology study; nonblinded	II
Nelson et al[76]	1983	Treatment; randomized controlled trial; nonblinded; N=28	IV lasix 1 mg/kg vs IV isosorbide dinitrate 50-200 μg/kg/h	Hemodynamics	Improved CO on nitrates; lower CO for next 90 min after lasix	Physiologic study; small N	II
Nelson et al[77]	1983	Treatment; randomized controlled trial; nonblinded; N=20	IV NTG vs hydralazine followed by lasix 1 mg/kg	Hemodynamics	Lasix lowers CO; also, nitrate venodilation "preferred"	Physiology study; small N	II
Nelson et al[78]	1984	Treatment; randomized; N=20	Lasix 1 mg/kg initially, then IV nitroglycerin vs hydralzine	Hemodynamics	Lasix initially lowers stroke volume and increases SVR	Physiology study; small N	II
Kraus et al[79]	1990	Treatment; case series; N=33	ICU patients with pulmonary artery catheter; lasix 20, 40, or 80 given, depending on initial PCWP	PCWP	Furosemide transiently increases PCWP, but increase prevented with NTG	Small N, nonrandomized; patient with acute respiratory distress syndrome included as CHF	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Hoffman and Reynolds[80]	1987	Treatment; nonrandom; N=57	Out–of–hospital treatment of patients; A=nitroglycerin+lasix (15 patients); B=morphine+lasix (13 patients); C=all 3 drugs (15 patients); D=nitroglycerin and morphine (14 patients)	Changes in respiratory rate	Nitroglycerin and lasix most improved	Small N; multiple groups; respiratory rate is poor criterion standard; heterogeneous patients	III
Butler et al[81]	2004	Prognosis; case control; N=382	Association of medications and treatment with increased creatinine >0.3 mg/dL	Worsening renal function during hospitalization	Higher loop diuretic doses and calcium channel blocker use associated with worsening renal function	Confounding variables but no obvious flaw	III
Fonarow et al[82]	2005	Prognosis registry; retrospective; N=65,000	Classification and regression tree analysis of registry database; derivation and validation cohorts	39 clinical variables analyzed	Inhospital mortality predicted by baseline BUN, creatinine, and systolic blood pressure	Strength of findings supported by both a derivation and validation cohort	II
Krumholz et al[83]	2000	Prognosis; retrospective; N=1,681 from 18 hospitals	Searched for principal diagnosis of CHF in Medicare file; standardized data abstraction	Incidence of worsening renal function	Worsening renal function associated with increased inhospital mortality (OR=2.7, 95% CI 1.6-4.6)		II
Smith et al[84]	2003	Prognosis; retrospective; N=412	Prospectively identified hospitalized CHF patients; data abstraction to assess for worsening renal function	6-month mortality vs worsening renal function of 0.1 to 0.5 mg/dL during hospitalization	Stepwise increase in risk of death with worsening renal function		II

ABG, arterial blood gas; *ACS*, acute coronary syndrome; *AUC*, area under the curve; *BMI*, body mass index; *BNP*, B-type natriuretic polypeptide; *BP*, blood pressure; *BUN*, blood urea nitrogen; *CCU*, cardiac care unit; *CHF*, congestive heart failure; *CI*, confidence interval; *CK*, creatine kinase; CO_2, carbon dioxide; *CPAP*, continuous positive airway pressure; *COPD*, chronic obstructive pulmonary disease; *Cr*, creatine; *CrCl*, creatinine clearance; *CVP*, central venous pressure; *ED*, emergency department; *FDA*, Food and Drug Administration; *GFR*, glomerular filtration rate; *h*, hour; *ICU*, intensive care unit; *lpm*, liters per minute; *IVP*, intraventricular pressure; *JVP*, jugular venous pressure; *LV*, left ventricle; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infarction; *min*, minute; *NYHA*, New York Heart Association; *NIH*, National Institutes of Health; *NP*, natriuretic peptide; *NIPSV*, noninvasive pressure support ventilation; *NP*, natriuretic peptide; *NTG*, nitroglycerin; O_2, oxygen; *OR*, odds ratio; PaO_2, partial pressure of oxygen; *PAOP*, pulmonary artery occlusion pressure; *PAP*, pulmonary artery pressure; *PCWP*, pulmonary capillary wedge pressure; PCO_2, partial pressure of carbon dioxide; PO_2, partial pressure of oxygen; *r*, coefficient of correlation; *RV*, right ventricle; *SOB*, shortness of breath; *SVR*, systemic vascular resistance; *VA*, Veteran's Affairs; *vs*, versus; *WHO*, World Health Organization; *y*, year.

Appendix A. Literature classification schema.*

Design/Class	Therapy†	Diagnosis‡	Prognosis§
1	Randomized, controlled trial or meta-analyses of randomized trials	Prospective cohort using a criterion standard	Population prospective cohort
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.
†Objective is to measure therapeutic efficacy comparing ≥2 interventions.
‡Objective is to determine the sensitivity and specificity of diagnostic tests.
§Objective is to predict outcome including mortality and morbidity.

Appendix B. Approach to downgrading strength of evidence.

	Design/Class		
Downgrading	**1**	**2**	**3**
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X