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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ABSTRACT

This clinical policy from the American College of Emergency Physicians is a revision of the 2007 "Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department with Acute Heart Failure Syndromes." A writing subcommittee conducted a systematic review of the literature to derive evidence-based recommendations to answer the following clinical questions: (1) In adult patients presenting to the emergency department with suspected acute heart failure syndrome, is the diagnostic accuracy of point-of-care lung ultrasound sufficient to direct clinical management? (2) In adult patients presenting to the ED with suspected acute heart failure syndrome, is early administration of diuretics safe and effective? (3) In adult patients presenting to the ED with suspected acute heart failure syndrome, is vasodilator therapy with high-dose nitroglycerin administration safe and effective? (4) In adult patients presenting to the ED with symptomatic acute heart failure syndrome, is there a defined group that may be discharged directly home for outpatient follow-up? Evidence was graded, and recommendations were made on the basis of the strength of the available data.

INTRODUCTION

Heart failure continues to be a significant diagnosis that affects individuals in the United States at epidemic proportions, and its prevalence is growing. The prevalence of heart failure among adults in the United States has increased by nearly 10% between 2012 (5.7 million Americans) and 2016 (6.2 million Americans). It is estimated that this prevalence will increase by another 46% by 2030 to more than 8 million individuals.[1]

Acute heart failure syndrome is a common condition encountered in the emergency department (ED), and it is associated with a 12% mortality rate during the inhospital treatment period.[2] Although survival after receiving a diagnosis of heart failure has improved slightly since 2012, 30-day, 1-year, and 5-year case fatality rates after hospitalization for heart failure remain high at 10%, 22%, and 42%, respectively.[1] The cost of this disease to the US health system is high and is expected to grow. In 2012, the total cost associated with heart failure was estimated to be $30 billion, and it is expected to increase to approximately $70 billion by 2030.[1]

The large heterogeneity of disease among patients with acute heart failure 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 of, epidemiology of, pathophysiology of, and therapy for acute heart failure. The term "acute heart failure syndromes" (AHFS) emerged from the 2004 and 2005 meetings of an international workgroup that was convened primarily to establish uniform terminology and definitions for heart failure.[3,4] The workgroup defined AHFSs as the "gradual or rapid deterioration in heart failure signs and symptoms resulting in a need for urgent therapy."[3] 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.[3] Despite the need for standardization, these terms and definitions do not appear to have been more widely adopted in the literature since their initial publication.[3] Terms such as "acute decompensated heart failure" and "acute heart failure" are still used frequently in the literature, and for the purposes of this policy, are considered interchangeable. For consistency purposes, the subsequent discussion of individual studies in this policy will use the term AHFS.

Appreciation of the heterogeneity in AHFS is important in the care of each individual patient. The ED plays a critical role in managing AHFSs because approximately 80% of patients who are hospitalized for the condition are admitted through the ED. The comparison of studies to date has been made more challenging by the lack of consensus on 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 patients with heart failure presenting to an ED by answering 4 critical questions representing the current interest or controversy.

METHODOLOGY

This American College of Emergency Physicians' (ACEP) clinical policy is based on a systematic review and critical descriptive analysis of the medical literature and is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[5]

Search and Study Selection

This clinical policy is based on a systematic review with a critical analysis of the medical literature meeting the inclusion criteria. Searches of PubMed, SCOPUS, Embase,

Web of Science, and the Cochrane Database of Systematic Reviews were performed by a librarian. Search terms and strategies were peer-reviewed by a second librarian. All searches were limited to human studies published in English. Specific key words/phrases, years used in the searches, dates of searches, and study selection are identified under each critical question. In addition, relevant articles from the bibliographies of the included studies and more recent articles identified by committee members and reviewers were included.

Two subcommittee members independently read the identified abstracts to assess them for possible inclusion. Of those identified for potential inclusion, each full-length text was reviewed for eligibility. Those identified as eligible were subsequently forwarded to the committee's methodology group (emergency physicians with specific research methodological expertise) for methodological grading using a Class of Evidence framework (Appendix E1, available at http://www.annemergmed.com).

Assessment of Risk of Bias and Determination of Classes of Evidence

Each study identified as eligible by the subcommittee was independently graded by 2 methodologists. Grading was done with respect to the specific critical questions; thus, the Class of Evidence grade for any one study may vary according to the question for which it is being considered. For example, an article that is graded an "X" because of "inapplicability" for one critical question may be considered perfectly relevant for another question and graded I to III. As such, it was possible for a single article to receive a different Class of Evidence grade when addressing a different critical question.

Design 1 represents the strongest possible study design to answer the critical question of whether the focus was therapeutic, diagnostic, prognostic, or a meta-analysis. Subsequent design types (ie, Design 2 and Design 3) represent respectively weaker study designs. Articles are then graded on dimensions related to the study's methodologic features and execution, including but not limited to randomization processes, blinding, allocation concealment, methods of data collection, outcome measures and their assessment, selection and misclassification biases, sample size, generalizability, data management, analyses, congruence of results and conclusions, and potential for conflicts of interest.

Using a predetermined process that combines the study's design, methodologic quality, and applicability to the critical question, 2 methodologists independently assigned a preliminary Class of Evidence grade for each article.

Articles with concordant grades from both the methodologists received that grade as their final grade. Any discordance in the preliminary grades was adjudicated through discussion which involved at least 1 additional methodologist, resulting in a final Class of Evidence assignment (ie, Class I, Class II, Class III, or Class X) (Appendix E2 (available at http://www.annemergmed. com)). Studies identified with significant methodologic limitations and/or ultimately determined to not be applicable to the critical question received a Class of Evidence grade of "X" and were not used in formulating recommendations for this policy. However, the content in these articles may have been used to formulate the background and to inform expert consensus in the absence of evidence. Question-specific Classes of Evidence grading may be found in the Evidentiary Table included at the end of this policy (Appendix E5).

Translation of Classes of Evidence to Recommendation Levels

In accordance with the strength of evidence for each critical question, the subcommittee drafted the recommendations and supporting text synthesizing the evidence using the following guidelines:

Level A recommendations. Generally accepted principles for patient care that reflect a high degree of scientific certainty (eg, based on evidence from 1 or more Class of Evidence I or multiple Class of Evidence II studies that demonstrate consistent effects or estimates).

Level B recommendations. Recommendations for patient care that may identify a particular strategy or range of strategies that reflect moderate scientific certainty (eg, based on evidence from 1 or more Class of Evidence II studies or multiple Class of Evidence III studies that demonstrate consistent effects or estimates).

Level C recommendations. Recommendations for patient care that are based on evidence from Class of Evidence III studies or, in the absence of adequate published literature, based on expert consensus. In instances where consensus recommendations are made, "consensus" is placed in parentheses at the end of the recommendation.

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 consistency of results, uncertainty of effect magnitude, and publication bias, among others, might lead to a downgrading of recommendations. When possible, clinically oriented statistics (eg, likelihood ratios [LRs], number needed to treat) are presented to help the

reader better understand how the results may be applied to the individual patient. This can assist the clinician in applying the recommendations to most patients but allow adjustment when applying to patients with extreme degrees of risk (Appendix E3 (available at http://www.annemergmed.com)).

Evaluation and Review of Recommendations

Once drafted, the policy was distributed for internal review (by members of the entire committee), followed by an external expert review and an open comment period for all ACEP membership. Comments were received during a 60-day open comment period with notices of the comment period sent electronically to ACEP members, published in *EM Today*, posted on the ACEP website, and sent to other pertinent physician organizations. The responses were used to further refine and enhance this clinical policy, although responses do not imply endorsement. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology, methodology, or the practice environment changes significantly.

Application of the Policy

This policy is not intended to be a complete manual on the evaluation and management of adult patients with AHFS but rather a focused examination of critical questions that have particular relevance to the current practice of emergency medicine. The potential benefits and harms of implementing recommendations are briefly summarized within each critical question.

It is the goal of the Clinical Policies Committee to provide evidence-based recommendations when the scientific literature provides sufficient quality information to inform recommendations for a critical question. When the medical literature does not contain adequate empirical data to inform a critical question, the members of the Clinical Policies Committee believe that it is equally important to alert emergency physicians to this fact.

This clinical policy is not intended to represent a legal standard of care for emergency physicians. The recommendations offered in this policy are not intended to represent the only diagnostic or management options available to the emergency physician. ACEP recognizes the importance of the individual physician's judgment and patient preferences. This guideline provides clinical strategies for which medical literature exists to inform the critical questions addressed in this policy. ACEP funded this clinical policy.

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

Inclusion Criteria. This guideline is intended for adult patients presenting to the ED with suspected AHFS.

Exclusion Criteria. This guideline is not intended for patients presenting with acute ST-elevation myocardial infarction, high-output heart failure, cardiogenic shock, renal failure, valvular emergencies, pregnant patients, or pediatric patients.

CRITICAL QUESTIONS

1. In adult patients presenting to the emergency department with suspected acute heart failure syndrome, is the diagnostic accuracy of point-of-care lung ultrasound sufficient to direct clinical management?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Use point-of-care lung ultrasound as an imaging modality in conjunction with medical history and physical examination to diagnose acute heart failure syndrome when diagnostic uncertainty exists as the accuracy of this diagnostic test is sufficient to direct clinical management.*

Level C recommendations. None specified.

Potential Benefit of Implementing the Recommendations:
- Lung ultrasound provides greater diagnostic accuracy for acute heart failure syndrome than standard care.
- Improved time to diagnosis and treatment.

Potential Harm of Implementing the Recommendations:
- Lack of proficiency in lung ultrasound imaging could lead to misdiagnosis.

Key words/phrases for literature searches: acute decompensated heart failure, acute diastolic heart failure, acute disease, acute heart failure, acute systolic heart failure, diagnostic imaging, echography, ED, emergencies, emergency, emergency care, emergency department, emergency health service, emergency medical services, emergency medicine, emergency room, emergency service, hospital emergency service, emergency services, emergency treatment, emergency ward, ER, heart failure, diastolic heart failure, systolic heart failure, hospital emergency service, lung, lung edema, lung POCUS, pulmonary ultrasonography, pulmonary US, ultrasonography, ultrasound, and variations and combinations of the key words/

*Use of lung ultrasound requires that the equipment is available, and the physician is proficient in its use.

phrases. Searches included January 2007 to search dates of July 5, 2019, and June 17, 25, 26, and 29, 2020.

Study Selection: Five hundred three articles were identified in the searches. Sixteen articles were identified from the search results as candidates for further review. After grading for methodologic rigor, 0 Class I studies, 1 Class II study, and 8 Class III studies were included for this critical question (Appendix E4 (available at http://www.annemergmed.com)).

The use of lung ultrasound (LUS) to diagnose AHFS holds many benefits. LUS is a low-cost, rapid, nonionizing imaging modality available at the bedside. LUS does not require an inordinate amount of training or experience to become proficient, and it has been demonstrated to be more accurate than a chest x-ray (CXR) in diagnosing pulmonary edema.[6,7] A diagnostic strategy incorporating bedside ultrasound has been shown to be superior in helping identify the correct diagnosis for undifferentiated dyspneic patients compared with a standard diagnostic strategy that did not incorporate ultrasound.[8] The use of bedside ultrasound, specifically in the evaluation of AHFS, is currently endorsed by the Society for Academic Emergency Medicine/Heart Failure Society of America's Acute Heart Failure Working Group, and by the European Society of Cardiology's consensus statement and heart failure guidelines (2015 and 2016).[4,9] This critical question evaluates the ability of LUS to accurately diagnose AHFS. If it can, LUS would be assumed sufficient to reliably make the diagnosis in settings of diagnostic uncertainty after history and physical alone.

Diagnostic strategies that incorporate LUS have consistently been shown to be superior to evaluations without LUS in diagnosing AHFS.[10-18] A detailed review of the primary literature revealed a single Class II systematic review and meta-analysis (SRMA), 3 Class III SRMAs, and 5 Class III studies that reported data pertinent to answering the critical question.

In a 2018 Class II SRMA, McGivery et al[10] examined the accuracy of LUS in diagnosing AHFS among undifferentiated dyspneic ED patients. The systematic review included 7 studies and a meta-analysis performed with a total sample of 1,861 patients. The pooled sensitivity and specificity for ED LUS for the diagnosis of AHFS were 82.5% and 83.6%, respectively, with a positive LR of 4.84 and a negative LR of 0.19. However, there was significant heterogeneity among the included studies. For this reason, a second meta-analysis was performed, which included attending physicians only (excluded medical students and residents) and showed a sensitivity and specificity for ED LUS in the diagnosis of AHFS of 88.6% and 83.2%, respectively. Two studies included in this review found high inter-rater reliability when comparing novice sonographers to experts (k=82% and 92%, respectively). Further, one included study found that the LUS scans were completed in less than 1 minute, although another found that it was completed in less than 5 minutes.

In a Class III SRMA, Martindale et al[11] examined the diagnostic elements available to emergency physicians for the diagnosis of AHFS, including history and physical examination, ECG, CXR, natriuretic peptides, LUS, bedside echocardiogram, and bioimpedance. The diagnostic performance of LUS was shown to be superior to other diagnostic modalities. This SRMA included a total of 8 studies examining LUS for the diagnosis of AHFS in a total sample population of 1,918 patients. LUS was found to have a pooled sensitivity and specificity of 85.3% and 92.7%, respectively, with a positive LR of 7.4 and a negative LR of 0.16. Comparatively, in this review, CXR was found to have a sensitivity of 56.9% and a positive LR of 4.8, and B-type natriuretic peptide (BNP) at a cutoff of <100 pg/mL was found to have a pooled sensitivity of 93.5%, a specificity of 52.9%, and a negative LR of 0.2. Bedside echocardiography identifying reduced ejection fraction was found to have a sensitivity and specificity of 80.6% for the diagnosis of AHFS with a positive LR of 4.1 and a negative LR of 0.24.

In a Class III SRMA, Staub et al[12] examined the accuracy of LUS in the diagnosis of AHFS, chronic obstructive pulmonary disease/asthma, and pneumonia. This SRMA included 14 studies with a total sample population of 2,778 patients, where most patients were recruited from the ED. Overall, the diagnostic accuracy of LUS for AHFS had an area under the curve of 0.91. This SRMA reported that the unpooled sensitivities and specificities for LUS ranged among studies from 75% to 90% for sensitivity and from 80% to 90% for specificity. In a second Class III SRMA, Lian et al[13] examined the accuracy of LUS for the diagnosis of AHFS in the ED. Fifteen studies were included, with a total of 3,309 patients. The meta-analysis found that the sensitivity and specificity were 85% and 91%, respectively; the positive LR was 8.94, and the negative LR was 0.14. The area under the curve was 0.91. All 4 SRMAs included the study by Pivetta et al[14] from 2015, which had a sample size of 1,005 patients. This study has also been reviewed separately as independent, primary literature. Table 1 summarizes the diagnostic performance of LUS for AHFS among the different meta-analyses.

Three Class III studies directly compared the accuracy of LUS versus CXR with or without natriuretic peptides. In a 2019 diagnostic study of 518 patients by Pivetta et al,[15] the investigators compared the diagnostic accuracy of LUS versus CXR and natriuretic peptides in addition to clinical evaluation. This multicentered, parallel, randomized control

Table 1. Summary of the diagnostic performance of LUS for AHFS as reported in 4 meta-analyses. Comparison of sensitivity, specificity, and LR of the included meta-analysis.

Study	Sensitivity (95% CI), %	Specificity (95% CI), %	Positive LR (95% CI)	Negative LR (95% CI)
McGivery et al[10] (2018) Class II N=1,861	82.5 (66.4-91.8)	83.6 (72.4-90.8)	4.84 (2.57-9.09)	0.19 (0.09-0.39)
Martindale et al[11] (2016) Class III N=1,918	85.3 (82.8-87.5)	92.7 (90.9-94.3)	7.4 (4.2-12.8)	0.16 (0.05-0.51)
Lian et al[13] (2018) Class III N=3,309	85 (84-87)	91 (89-92)	8.94 (5.64-14.18)	0.14 (0.08-0.26)
Staub et al[12] (2019) Class III N=2,778	(75-90)	(80-90)	Not Available	Not Available

trial included all adult patients presenting with a complaint of acute or acute on chronic dyspnea. After hospital discharge or death, 2 independent physicians (ie, an intensivist and emergency physician) reviewed the charts to adjudicate the etiology of the dyspnea. The accuracy of the diagnosis of AHFS by clinical examination alone did not differ between the 2 arms. However, LUS was found to be more accurate than clinical evaluation alone and more accurate than the combination of the clinical examination, CXR, and natriuretic peptides. In addition, notable in this study is the fact that the strategy of CXR combined with natriuretic peptides did not significantly increase the diagnostic accuracy compared with clinical evaluation alone. The authors concluded that the approach that used LUS reduced diagnostic errors in 8% of patients and the median time to diagnosis from 104.5 minutes to 5 minutes.

In an earlier, prospective, multicenter, Class III study of 1,005 patients, Pivetta et al[14] (2015) reported an improved diagnosis of AHFS using LUS. In this study of adult patients with acute or acute on chronic dyspnea, patients had a standard workup followed by questioning of the examining physician as to whether they believed that the cause of the dyspnea was because of AHFS. Then, LUS was performed, and the presumptive diagnosis was reassessed. Following discharge, the patient's final diagnosis was adjudicated by an emergency physician and a cardiologist, both of whom were blinded to the LUS results. Standard clinical workup was shown to be inferior to a diagnostic strategy that incorporated LUS for the diagnosis of AHFS (Table 2). However, LUS alone was also shown to be superior to both CXR and natriuretic peptides (ie, BNP/ NT-prop-BNP) in the diagnosis of AHFS.

This study was followed by another Class III study by Sartini et al.[16] In this prospective single-center observational cohort study of 236 adult patients with acute or acute on chronic dyspnea, the investigators examined the diagnostic accuracy of LUS, CXR, and NT-pro-BNP in the diagnosis of AHFS. Emergency physicians skilled in LUS performed the examinations and were blinded to all other aspects of patient care. The sensitivity of LUS reported in this study of 57.73% was lower than that reported in other studies. However, a subgroup analysis of LUS performance among patients who did not receive pre-hospital diuretics found that the sensitivity of LUS was 83%, which is consistent with the sensitivity reported in other studies. The transport times were not disclosed in the study; hence, it is difficult to assess how likely it was for the administration of a diuretic to affect the findings on LUS.

In a Class III single-center observational cohort in Thailand, Nakornchai et al[17] assessed whether multiorgan point-of-care ultrasound (POCUS) performed by emergency medicine residents could be used to improve the diagnostic accuracy of AHFS. This study has major limitations and excludes patients with myocardial infarction, shock, or those receiving positive pressure ventilation. Furthermore, its main outcome was the diagnostic accuracy of multiorgan POCUS instead of solely examining the diagnostic accuracy of LUS for AHFS. These limitations could explain the uniquely poor sensitivity (35%) reported for LUS in diagnosing AHFS in this study compared with those in the other examined literature, although the specificity (72.7%) reported is consistent with that of other examined literature.

In a Class III, multicenter, prospective, observational cohort study, Buessler et al[18] examined the use of LUS in addition to the Brest score (clinical decision tool for diagnosing heart failure) in diagnosing AHFS. This study found that LUS increased diagnostic accuracy in addition to the Brest score, both in the whole patient population and in patients with intermediate Brest scores.

Table 2. Standard clinical workup versus diagnostic strategy with LUS to diagnose AHFS. Comparison of sensitivity, specificity, PPVs, NPVs, LR, and AUC of the included studies.

Study	Design	Diagnostic Approach	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV (95% CI), %	NPV (95% CI), %	Positive LR (95% CI)	Negative LR (95% CI)	AUC (95% CI)
Pivetta et al[15] (2019) N=518 Class III	Multicentered randomized controlled trial study	LUS CXR/NT-pro-BNP	93.5 (87.7-97.2) 85 (76.5-91.4)	95.5 (90.5-98.3) 89.4 (83.5-93.7)	95.1 (89.6-98.2) 83.3 (74.7-90.0)	94.1 (88.7-97.4) 90.5 (84.8-94.6)	20.9 (9.54-45.7) 8.0 (5.1-12.6)	0.07 (0.03-0.13) 0.17 (0.11-0.27)	0.95 0.87
Pivetta et al[14] (2015) N=1,005 Class III	Prospective multicentered observational cohort study	Clinical Workup LUS-Implemented LUS Alone CXR	85.3 (81.8-88.4) 97 (95-98.3) 90.5 (87.4-93) 69.5 (65.1-73.7)	90 (87.2-92.4) 97.4 (95.7-98.6) 93.5 (91.1-95.5) 82.1 (78.6-85.2)	88 (84.6-90.8) 97 (95-98.3) 92.3 (89.4-94.6) 76.8 (72.5-80.8)	87.8 (84.8-90.4) 97.4 (95.7-98.6) 92 (89.4-94.1) 75.9 (72.5-79.3)	8.6 37.5 14 3.9	0.2 0.03 0.1 0.4	87.6 0.97 0.92 0.76
Pivetta et al[14] (2015) Subgroup analysis N=486		LUS-Implemented BNP/NT-pro-BNP LUS-alone	97.5 (94.9-99) 85 (80.3-89) 89.3 (85.1-92.7)	95.6 (91.9-98) 61.7 (54.6-68.3) 89.8 (84.8-93.6)	96.8 (94-98.5) 75.1 (69.9-79.7) 92.3 (88.4-95.1)	96.6 (93.1-98.6) 75.1 (67.9-81.6) 86 (80.7-90.4)	22.3 2.2 8.8	0.02 0.20 0.11	0.97 0.73 0.90
Sartini et al[16] (2017) N=236 Class III	Prospective single-centered observational cohort study	LUS CXR NT-pro-BNP >300 pg/mL LUS subgroup without prehospital diuretics N=181	57.73 (47.28-67.7) 74.49 (64.69-82.76) 97.59 (91.57-99.71) 83	87.97 (81.2-92.96) 86.26 (79.16-91.65) 27.56 (20.01-36.19) 86.39	77.78 (66.4-86.73) 80.22 (70.55-87.84) 46.82 (39.21-54.54) Not Available	74.05 (66.49-80.69) 81.88 (74.43-87.92) 94.59 (81.81-99.34) Not Available	4.8 (2.94-7.83) 5.42 (3.48-8.45) 1.35 (0.20-1.51) Not Available	0.48 (0.38-0.61) 0.30 (0.21-0.42) 0.09 (0.02-0.35) Not Available	0.84 Not Available 0.76 Not Available

PPV, positive predictive value; *NPV*, negative predictive value

Summary

In patients presenting with acute dyspnea and the possible diagnosis of AHFS, evidence supports the use of POCUS to improve diagnostic accuracy and help direct management. The presence of B-lines on bedside ultrasound is an independent predictor of AHFS. When combined with historical information and physical examination findings, bedside ultrasound outperforms chest radiography and laboratory testing, including natriuretic peptides.

Future Research

To date, no studies have evaluated if more rapid diagnosis of acute decompensated heart failure using LUS significantly alters important clinical patient-centered outcomes. A randomized control trial that compares the use of LUS to identify B-lines versus usual care on outcomes such as the need for intubation, ICU admissions, and mortality would be the next logical step. Additionally, randomized control trials are also needed to examine whether the use of a multimodal POCUS strategy significantly improves the standard diagnostic workup for patients being considered for the diagnosis of AHFS in ED.[19,20]

2. In adult patients presenting to the emergency department with suspected acute heart failure syndrome, is early administration of diuretics safe and effective?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Although no specific timing of diuretic therapy can be recommended, physicians may consider earlier administration of diuretics when indicated for emergency department patients with acute heart failure syndrome, because it may be associated with reduced length of stay and inhospital mortality (consensus recommendation).

Physicians should be confident in the diagnosis of acute heart failure syndrome with volume overload in a patient before the administration of diuretics because treatment with diuretics may cause harm to those with an alternative diagnosis (consensus recommendation).

Potential Benefit of Implementing the Recommendations:
- Decrease delays in treatment of concomitant conditions.
- Decrease length of stay and inpatient mortality.

Potential Harm of Implementing the Recommendations:
- Giving diuretics too early to a patient who is ultimately proven not to have the diagnosis of acute heart failure syndrome or when the patient is not experiencing volume overload as a cause of their acute heart failure syndrome could be harmful.

Key words/phrases for literature searches: acute decompensated heart failure, acute diastolic heart failure, acute heart failure, acute systolic heart failure, diuretic, diuretic agent, diuretics, ED, emergencies, emergency care, emergency department, emergency health service, emergency medical services, emergency medicine, emergency room, emergency service, emergency services, emergency treatment, emergency ward, ER, heart failure, and hospital emergency service. Searches included January 2007 to search dates of July 8, 2019, and June 22, 25, and 29, 2020.

Study Selection: Five hundred eighty-three articles were identified in the searches. Eleven articles were identified from the search results as candidates for further review. After grading for methodologic rigor, zero Class I studies, zero Class II studies, and 1 Class III study was included for this critical question (Appendix E4).

The use of loop diuretics in the management of acute heart failure induces an increase in sodium and water excretion by the kidney, thus reducing preload on the heart. It has been an integral component of the multimodal management of patients with acute heart failure with volume overload in the ED for the last 40 years. The management of patients with euvolemic or hypovolemic heart failure is more complex and typically requires alternative therapeutic strategies; however, this is beyond the scope of the critical question reviewed. When a patient with heart failure is determined to be volume overloaded (eg, history consistent with volume overload, cardiomegaly, pleural effusions, leg swelling, weight gain, etc), the loop diuretics that are frequently administered are furosemide, torsemide, and bumetanide. The pharmacodynamics differ between these medications when given intravenously, with furosemide having the least potency, followed by torsemide and bumetanide. Torsemide and bumetanide have similar bioavailability, which is higher than that of furosemide. The time to peak effect for these medications ranges from 15 minutes for bumetanide to 30 minutes for furosemide and 60 minutes for torsemide. Despite the known pharmacodynamics of these medications, their optimal timing of administration in the ED and the subsequent effect on clinical outcomes are unclear.

Defining "early" treatment in the ED is difficult because of various definitions in the literature. There has not been a widely accepted time of administration with regards to diuretics in AHFS as there has been with therapies for other disease processes. Further confounding the "early administration" of diuretics is the fact that heart failure is not easy to quickly identify among undifferentiated patients in the ED. Some patients ultimately require admission to the hospital and further studies such as echocardiography before a more definitive diagnosis can be made. Most patients who receive "early" identification and treatment tend to be those who have had previous episodes of established AHFS and develop similar symptoms or those with more severe and classic symptoms. Therefore, with regards to our search on this question, we purposely did not define "early" by a specific time cutoff but rather left it undefined to help ensure that we captured all applicable literature. Unfortunately, many of the studies that have addressed the question of the timing of administration have been of limited quality and/or not applicable to the United States ED population.

In a Class III, observational trial, Wong et al,[21] did not find an association between treatment delays and 30-day all-cause mortality or readmission. However, they did find an association between treatment delays and other outcomes. This study was a retrospective secondary analysis of 6,971 patients from the Acute Decompensated Heart Failure Registry Emergency Module (ADHERE-EM). Patients aged 65 years and older who were hospitalized for AHFS and received intravenous heart failure therapy at the initial visit were studied. The median time to intravenous heart failure therapy was 2.3 hours (1.1 to 4.4 hours), with an incidence of 30-day all-cause mortality or readmission of 27.4%. The time to treatment had no clinically significant association with 30-day all-cause mortality (hazard ratio 1.00; 95% confidence interval [CI] 1.00 to 1.01) or with 30-day all-cause readmission (hazard ratio 1.00; 95% CI, 0.99 to 1.00). An increasing time to treatment was associated with a very small increased risk of inhospital mortality (odds ratio 1.01; 95% CI 1.00 to 1.02) and an approximate 1.4-hour increase in the index admission length of stay. This included treatments with a diuretic alone and combinations of a diuretic with an inotrope or vasoactive medication. However, it is important to note that these statistically significant results are unlikely clinically significant. They did perform a subset cohort analysis, including those patients who did receive a diuretic or a diuretic and another agent. In those patients receiving diuretics alone, there was also no difference in all-cause mortality at 30 days.

Summary

Only one weaker, Class III study was identified that met the criteria and helped to answer this critical question. Therefore, it is difficult to make confident recommendations related to the timing of diuretic therapy in patients with AHFS. The decision to treat early is complicated by the fact that rapidly and accurately identifying AHFS is often difficult, and administration of diuretics to patients without volume overload and a diagnosis of acute heart failure may cause harm.

Future Research

Future research should involve randomization of patients presenting to the ED with suspected acute heart failure to treatment with intravenous diuretics at clearly defined time intervals with clinically significant outcome measures such as hypotension, kidney injury, need for escalation of therapy or level of monitoring, length of stay, and mortality. Research should also focus on factors that help to accurately and rapidly diagnose AHFS.

3. **In adult patients presenting to the emergency department with suspected acute heart failure syndrome, is vasodilator therapy with high-dose nitroglycerin administration safe and effective?**

Patient Management Recommendations

Level A recommendations. None specified.
Level B recommendations. None specified.
Level C recommendations. Consider using high-dose nitroglycerin as a safe and effective treatment option when administered to patients with acute heart failure syndrome and elevated blood pressure (Consensus recommendation).*

Potential Benefit of Implementing the Recommendations:
- This therapy has the potential benefit of reducing respiratory distress and decreasing the need for endotracheal intubation and ICU admission.

Potential Harm of Implementing the Recommendations:
- High-dose nitrates could potentially produce hypotension.

Key words/phrases for literature searches: acute decompensated heart failure, acute diastolic heart failure,

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*Although nitroglycerin infusions of up to 400 mcg/min have been described as "standard dosing," some may consider a dosage of 200 mcg/min or higher as "high dose."[22] "High dose" nitroglycerin has also been described as bolus intravenous dosing of 2,000 mcg every 3 to 5 minutes.[22]

acute disease, acute heart failure, acute systolic heart failure, ED, emergencies, emergency, emergency care, emergency department, emergency health service, emergency health services, emergency medicine, emergency room, emergency service, emergency services, emergency treatment, emergency ward, ER, glyceryl triturate, heart failure, hospital emergency service, nitroglycerin, and variations and combinations of the key words/phrases. Searches included January 2007 to search dates of July 12 and 15, 2019, and June 23, 25, and 29, 2020.

Study Selection: One hundred seventy-seven articles were identified in the searches. Fifteen articles were identified from the search results as candidates for further review. After grading for methodological rigor, zero Class I studies, zero Class II studies, and 1 Class III study was included for this critical question (Appendix E4).

Our knowledge of the pathophysiology of AHFS has evolved over the years. Although it was once thought that AHFS was simply a problem of volume overload, we now know that many cases are the result of cardiac dysfunction and excess vascular tone.[23] The majority of patients presenting with AHFS suffer from excess preload and an increased systemic vascular resistance (afterload), which is associated with a reduced cardiac output through systolic or diastolic dysfunction.[22] Vasodilators can reduce preload and afterload, resulting in improved cardiac output and reduced pulmonary congestion. The use of vasodilators has therefore been recommended in consensus statements for the emergency management of AHFS.[23,24]

Nitrates have been the preferred vasodilator in the management of AHFS for decades and are part of the standard recommended medication regimen for patients who are normotensive or hypertensive.[23,24] Nitrates decrease preload and, at higher doses, decrease afterload as well. The onset of vasodilatory effects is within 1 to 3 minutes, depending on the route of delivery, and the half-life is 2 to 7 minutes. Unfortunately, consensus statements and guidelines provide little direction as to the optimal dosing regimen of nitrates. ACEP's prior clinical policy pertaining to the evaluation and management of patients presenting to the ED with AHFS addressed whether vasodilator therapy should be prescribed in the ED for a patient with AHFS.[3] The 2007 clinical policy concluded with a Level B recommendation that intravenous nitrate therapy should be used; however, no specific dosage was recommended.

In the only Class III trial of the above studies, Levy et al[22] performed a nonrandomized open-label trial evaluating the use of 2,000 mcg intravenous bolus doses of nitroglycerin

every 3 to 5 minutes in patients with dyspnea and AHFS whose systolic blood pressure was greater than or equal to 160 mm Hg or whose mean arterial pressure was greater than or equal to 120 mm Hg and who were refractory to initial therapy. Initial therapy consisted of Class I recommendations from the American Heart Association's 2000 "Guidelines for the Evaluation and Management of Heart Failure," including high-flow oxygen, with 100% nonrebreather mask, sublingual nitroglycerin 400 mcg every 5 minutes up to a maximum of 4 treatments, and furosemide 60 to 80 mg intravenously.[25] Morphine sulfate 3 to 5 mg intravenous push was considered optional. If patients failed to improve after this initial therapy and the treating physician believed that the patient required intravenous nitroglycerin, consenting patients were included in the trial.

Trial patients received an intravenous infusion of nitroglycerin started at a dose of 0.3 to 0.5 mcg/kg per minute. The nitroglycerin infusion was increased at the discretion of the treating physician in increments of 20 mcg/min every 1 to 3 minutes to a maximum of 400 mcg/min. If the systolic blood pressure fell below 90 mm Hg, further increased dosage of the nitroglycerin was discontinued. If blood pressure did not improve, the nitroglycerin was stopped. Concurrent with the initiation of the nitroglycerin infusion and titration, all patients received an initial 2,000 mcg intravenous bolus of nitroglycerin, and repeat dosing of the 2,000 mcg intravenous boluses was allowed every 3 to 5 minutes at the discretion of the treating physician for a period of up to 30 minutes (maximum potential dose of 20 mg). The mean total dose of bolus-dose nitroglycerin was 6,500 mcg (±3,400 mcg).

The patients receiving high-dose nitroglycerin showed a trend toward improvement in the primary efficacy endpoint of reduced endotracheal intubations within 6 hours (13.8% [95% CI 4.8% to 29.5%] versus 26.7% [95% CI, 15.5% to 40.8%]), a trend toward improvement in the secondary endpoints of reduced need for bilevel positive airway pressure (6.9% [95% CI, 1.5% to 20.3%] versus 20.0% [95% CI 10.4% to 33.3%]), and an improvement in the secondary endpoint of reduced ICU admissions (37.9% [95% CI, 22.1% to 56.1%] versus 80.0% [95% CI, 66.7% to 89.6%]). A single episode of symptomatic hypotension occurred in the high-dose nitroglycerin group after a single bolus of 2 mg but resolved after a 500 mL intravenous bolus of fluid. No patient in either group developed immediate ECG changes of ischemia. Neither the high-dose nitroglycerin group nor the nonintervention group demonstrated any adverse neurologic events or inhospital deaths.

Summary

AHFS is a common ED presentation, often associated with ICU admission and endotracheal intubation. Guidelines and consensus statements now recognize the importance of cardiac and vascular dysfunction in the pathophysiology of AHFS, but specific recommendations regarding vasodilator therapy (medication, dosing regimen, etc) are lacking. The single Class III study noted above demonstrated the safety of high-dose nitroglycerin therapy in patients with AHFS while suggesting possible improvements in clinical outcomes, including reduced need for endotracheal intubation, bilevel positive airway pressure, and ICU admission without significant adverse effects.

Future Research

Given the frequency of AHFS presentations to the ED and its associated morbidity and mortality, it is critical that research continues to inform physicians about the optimal care for these patients. The current prevailing theory regarding the pathophysiology underlying many of these presentations focuses on excess preload and vascular tone dysfunction manifesting as excess afterload. Studies evaluating the use of high-dose nitrates to treat this vascular tone dysfunction have been favorable in their trend toward a larger magnitude of benefit; however, current studies are limited by their small numbers and their retrospective, nonrandomized, open-label designs. Larger studies using a prospective randomized, blinded protocol would be invaluable in clarifying whether high-dose nitrates can, in fact, produce rapid clinical benefits in selected patients with AHFS.

4. In adult patients presenting to the emergency department with symptomatic acute heart failure syndrome, is there a defined group that may be safely discharged home for outpatient follow-up?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Do not rely on current acute heart failure syndrome risk stratification tools alone to determine which patients may be discharged directly home from the emergency department.

Consider using the Ottawa Heart Failure Risk Scale (OHFRS) to help determine which higher-risk patients for adverse outcome should not be discharged home.

Level C recommendations. Consider using the Emergency Heart Failure Mortality Risk Grade for 7-day mortality (EHMRG7) or the STRATIFY decision tool to help determine which higher-risk patients for adverse outcome should not be discharged home.

Use shared decision-making strategies when determining the appropriate disposition of AHFS patients (Consensus recommendation).

Potential Benefit of Implementing the Recommendations:

- Emergency physicians may reduce the likelihood that a discharged patient experiences an adverse outcome during short-term follow-up.

Potential Harm of Implementing the Recommendations:

- Emergency physicians may increase the number of AHFS admissions to the hospital, which would potentially add to hospital overcrowding and negatively affect reported acute heart failure syndrome readmission metrics.
- More patients could experience complications associated with hospital admission.

Key words/phrases for literature searches: acute decompensated heart failure, acute diastolic heart failure, acute disease, acute heart failure, acute systolic heart failure, discharge, discharged, ED, emergencies, emergency, emergency care, emergency department, emergency health service, emergency medical services, emergency medicine, emergency room, emergency service, emergency services, emergency treatment, emergency ward, ER, heart failure, hospital discharge, hospital emergency service, patient discharge, and variations and combinations of the key words/phrases. Searches included January 2007 to search dates of July 15, 2019, and June 25 and 29, 2020.

Study Selection: Nine hundred thirty-eight articles were identified in the searches. Fourteen articles were identified from the search results as candidates for further review. After grading for methodological rigor, zero Class I studies, 1 Class II study, and 3 Class III studies were included for this critical question (Appendix E4).

Hospital admissions account for an estimated one-third of health care spending in the United States.[26] Approximately one-half of all hospital admissions in the United States originate from EDs.[26] Of the approximately $39.2 billion dollars spent on heart failure care in the United States each year, hospital admissions account for a total cost of more than $11 billion, and they represent the single largest proportion of the expenditure.[27,28] Patients with heart failure often have other comorbid conditions (eg, hypertension, ischemic heart disease, diabetes, chronic kidney disease, and atrial fibrillation), which may also contribute to admission decisions and prolong hospital

Figure 1. Ottawa Heart Failure Risk Scale (OHFRS).[32] (Used with permission). *EMS*, emergency medical services; *HR*, hazard ratio; *MI*, myocardial infarction; *TIA*, transient ischemic attack.

length of stay.[28,29] Heart failure is a relatively grave diagnosis because it is associated with a high 30-day, 1-year, and 5-year after hospitalization mortality of 10%, 22%, and 42%, respectively.[30] Although more than 80% of all ED visits in the United States result in the patient being discharged home, 82% of patients presenting with primary AHFS are admitted to the hospital for further care with a median inpatient length of stay of 3.4 days.[28,31] This differs from other countries such as Canada, where the admission rate of acute heart failure patients from the ED is estimated to be only 40 to 60%.[32] Patients admitted for heart failure have readmission rates as high as 30% to 60% within 3 to 6 months after discharge.[29]

Although more than 80% of all patients presenting to an ED in the United States with primary AHFS are admitted to the hospital, approximately one-half present with "low risk" features and are believed to be possibly unnecessary admissions.[29,31] The historical reluctance of emergency medicine physicians to discharge home a greater percentage of patients with acute heart failure could be the result of several factors, including the significant mortality associated with the disease, the relatively high associated complication rate, including readmissions, and the absence of any known discrete risk factors or decision rules that could help reliably establish which patients are safe to be discharged directly home from the ED. Establishing a low-risk group of AHFS patients who are safe for direct discharge from the ED could reduce health care costs, reduce the risk of nosocomial infections and other untoward events associated with hospital stays, improve the availability of hospital beds for sicker patients, and improve patient satisfaction.

Therefore, a comprehensive review of the medical literature was performed to learn if any data could be used to reliably define which patients presenting to an ED with the diagnosis of symptomatic AHFS could be safely discharged directly home. The literature review revealed 56 publications that were deemed potentially applicable to the critical question. After further analysis, 42 of these articles were assessed as not directly addressing the critical question. Fourteen studies were identified as pertinent, reviewed by the methodologists, and received grading. Of these 14 studies, 10 were considered fatally flawed, and 4 studies (1 Class II and 3 Class III) were considered contributory and received a grade.

In the only Class II study referred to as "RAD-2," Stiell et al[32,33] prospectively studied consecutive adult patients who presented to Canadian EDs with serious adverse events (SAEs) resulting from acute heart failure to assess the accuracy, acceptability, and potential effect of their previously derived OHFRS score (from the RAD-1 Study [Figure 1]) on a new population of patients.

The OHFRS score was developed to estimate the probability of SAEs in the subsequent 14 days after evaluation and treatment in the ED. In this study, the use of the OHFRS score at different cutoff points did not enable the identification of a group of patients who were reliably safe for discharge directly home. However, the score did perform better than standard physicians' decision-making in predicting which patients should not be discharged home because of their higher risk of serious adverse outcomes.

In this study, 4,999 patients presenting to the ED with shortness of breath were screened for eligibility. Of these, 3,130 were deemed ineligible and excluded from the study. Patients were excluded from the study if they were believed to be unstable or subjectively "too ill" to be considered for discharge after 2 to 12 hours of ED management. Of the 1,869 eligible patients, 769 were missed, primarily for presenting outside of the study hours, and 1,100 were enrolled in the study. The included patients had an OHFRS score calculated 2 to 12 hours after ED treatment. After calculating the OHFRS score, the staff was asked

which risk category the patient was in (ie, low, medium, high, very high) for an SAE and how comfortable they would be with using the scale to make a disposition decision (5-point scale from very comfortable to very uncomfortable).

The primary outcome was any SAE defined as: death from any cause within 30 days of the ED visit, any of the following within 14 days of the visit: admission to a monitored unit, endotracheal intubation or need for noninvasive ventilation (unless used at home), myocardial infarction, recipient of a major procedure (eg, percutaneous coronary intervention, cardiac surgery, or hemodialysis); or returning to the ED for any medical problem related to the initial presentation within 14 days resulting in admission to the hospital. Investigators assessing for SAEs were blinded to the OHFRS scores. Of the 1,100 enrolled patients, 684 received NT-proBNP testing (a component of the score) at their index evaluation.

Using their normal standard of care, researchers admitted 57.2% of patients to the hospital and discharged 42.8% from the ED at the index visit. The overall SAE rate was 15.5%, with 19.4% occurring among admitted patients and 10.2% among those discharged home. Of the 41 recorded deaths, 16 (39%) occurred among those patients who were discharged home. Using an OHFRS score cutoff of more than 1 among patients both without the NT-proBNP value as well as those with the value would have increased the sensitivity for the outcome of an SAE from approximately 70% using clinical judgment alone to 91.8% and 95.8%, respectively (still missing as many as 8% and as few as 4% of SAEs). However, this increased sensitivity would have also led to a 20% to 26% respective increase in the admission rate of the 2 groups of patients. Overall, the researchers reported that 11.9% of the time, they felt "uncomfortable" or "very uncomfortable" in using the OHFRS to make disposition decisions for their patients.

Although this study may be of the highest quality of the studies to date looking prospectively at predictors of outcomes among ED patients with AHFS, it still has several limitations, including intention bias because patients who were admitted to the hospital may be less likely to experience an SAE because of the closer monitoring, the fact that not all patients had NT-pro-BNP measured and not all patients received assessment while ambulating, the enrolled subjects were, for the most part, a convenience sample because some patients were not included because researchers were "too busy," and the fact that the study used the same academic EDs that derived the original OHFRS score. Although never mentioned, it is assumed that when NT-proBNP was not measured, a

score of "0" was used for this variable. Additionally, patients who were believed to be subjectively "too ill to be ready for discharge after 2 to 12 hours of ED management" were excluded; hence, we do not fully understand how the OHFRS would have performed if applied to all presenting AHFS patients. Also of note, adding a point on the scale when patients were too sick or never asked to do the walk test, as the investigators did, could falsely risk stratify the patient to a group of less risk than had the variable actually been assessed. Finally, because the study discharged patients home on the basis of the standard of physician gestalt, there is still no reliable data on how the OHFRS score would perform for discharge decision-making if it were the sole determinant for disposition.

Given the current data, including both the seriousness of the adverse outcomes assessed and the limitations of the study, the OHFRS score appears neither sensitive nor specific enough to be relied upon as the sole criteria by which emergency physicians could make disposition decision-making for their patients with AHFS. The sensitivity of the tool when all OHFRS variables are recorded does, however, hold promise for future study. It would be interesting to learn how the scale could affect care among patients with AHFS cared for by health care professionals in United States EDs, where admission rates are significantly higher. Still, knowledge of the different OHFRS variables and the different variables' performance in screening for the likelihood of an SAE could further aid emergency physicians in the disposition decision-making for their patients with AHFS.

Although the 2017 report by Stiell et al[32] of the OHFRS score, "RAD-2," is a better validated, prospectively studied report of the use of the OHFRS score, the original derivation Class III study by Stiell et al[33] of the score in 2013, "RAD-1," is notable for several reasons. First, the rate of admission for the patients with AHFS from the ED in RAD-1 was much lower (38.1% in the original study versus 57.2% in RAD-2), and the rates of SAEs were also slightly lower for both admitted patients (16% versus 19.4% in RAD-2) and discharged patients (9.0% versus 10.2% in RAD-2). Despite these facts, the diagnostic performance for the score remained relatively consistent between the RAD-1 and RAD-2 datasets for both sensitivity and specificity at the different point cutoffs of more than 1 and more than 2. This confirmation of the association between the score and the outcome of SAEs is reassuring that future applications of the score, at least in that region of hospitals, will likely yield similar results.

Of the 2 remaining Class III studies, only Collins et al[34] in 2015 reported meaningful outcomes beyond mortality
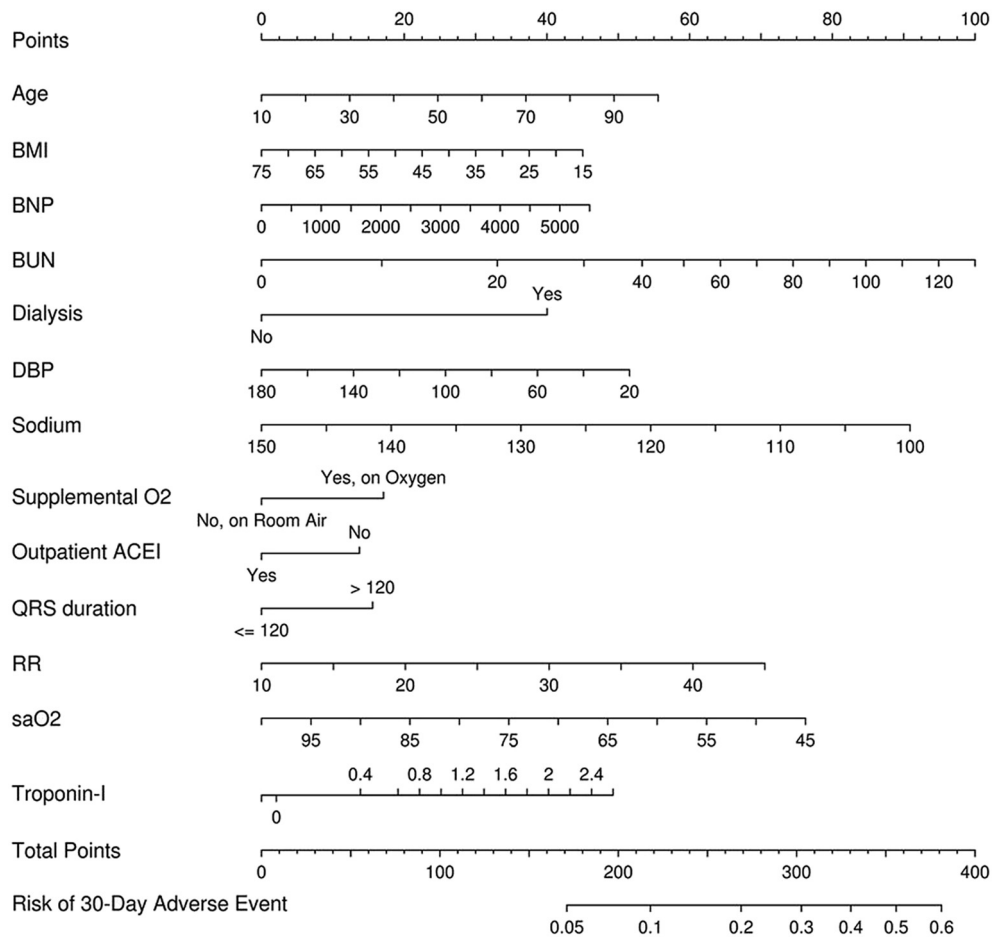
Figure 2. Nomogram for use of the STRATIFY decision tool.[34] (Used with permission).

alone. In this study, Collins et al derived the "STRATIFY" AHFS risk assessment tool from a final cohort of 1,033 ED patients with AHFS (Figure 2). The tool includes variables such as age, vital signs, use of oxygen/angiotensin-converting enzyme inhibitors/dialysis, ECG data, and laboratory data to assess risk.

The disposition decision of the original cohort of patients was at the discretion of the treating physicians and occurred independently of the STRATIFY tool results. Of the total 1,033 patients, 953 (92%) were admitted to the hospital, and 80 (8%) were discharged home. Patients were followed for 30 days and screened for the following adverse event outcomes: acute coronary syndrome/percutaneous coronary intervention/coronary artery bypass grafting, emergency dialysis, intubation, mechanical cardiac support, or death. The derived STRATIFY decision tool was used to identify patients at less than1%, 3%, and 5% risk of an adverse outcome. No patients were found to be at less than 1% risk for an adverse outcome. However, 1.4% (N=14) were found to have a less than 3% risk of an adverse

outcome, and 13% (N=134) were found to have a less than 5% risk of an adverse outcome. Among the 134 patients at less than 5% risk of an adverse event, it was determined that there was 1 death that occurred more than 5 days after the initial ED evaluation. When compared with the actual disposition of patients by the ED physicians, the authors determined that the use of the STRATIFY tool for disposition decision-making at a cutoff of less than 5% risk of an adverse event would have allowed for an additional 105 patients (10%) to be discharged home. This study had multiple limitations, including the potential for recruitment bias resulting from the convenience sample; 63 patients withdrew from the study, 18 patients were lost to follow-up, and the tool was only internally validated using bootstrap methods, so no external validation was performed. Additionally, the application of the STRATIFY tool is extremely challenging because it requires the drawing of perpendicular lines on a nomogram to assess the value of points for each variable and the overall 30-day risk of an adverse event. Finally, not only is a 5%

Variable	Units	Additive or Multiplicative Component
Age	y	2 × age
Transported by EMS	If "yes"	+60
SBP	mm Hg*	−1 × SBP
Heart rate	beats/min†	1 × heart rate
Oxygen saturation	%‡	−2 × oxygen saturation
Creatinine	mg/dL§	20 × creatinine
Potassium	4.0 to 4.5 mmol/L	0
	≥4.6 mmol/L	+30
	≤3.9 mmol/L	+5
Troponin	>ULN	+60
Active cancer	If "yes"	+45
Metolazone at home	If "yes"	+60
Adjustment factor‖		+12
Total		EHMRG score¶

EHMRG = Emergency Heart Failure Mortality Risk Grade; EMS = emergency medical services; SBP = systolic blood pressure; ULN = upper limit of normal.
* Initial/triage SBP, maximum of 160 mm Hg.
† Initial/triage heart rate, minimum of 80 beats/min and maximum of 120 beats/min.
‡ Lowest initial/triage oxygen saturation, maximum of 92%.
§ If creatinine concentration is in μmol/L, divide by 88.4 to convert to mg/dL.
‖ Adjustment factor of +12 added to allow for an approximate 0 median score.
¶ All variables are required to calculate the score; users are cautioned against estimating component values. The EHMRG is not for use in patients who are dialysis-dependent.

Figure 3. EHMRG 7-day mortality risk score.[36] (Used with permission).

risk of the serious adverse outcomes possibly too high to allow to occur but the 95% upper limit of the CI also extends to 10%.

In the last Class III article, Lee et al[35] derived and then prospectively validated the Emergency Heart Failure Mortality Risk Grade (EHMRG) for its ability to predict 7-day (EHMRG7) and 30-day (EHMRG30-ST) mortality among Canadian ED patients with AHFS. They then compared these results with clinicians' general gestalt of mortality risk. The EHMRG7 tool was derived and first reported in an earlier article by Lee[36] (Figure 3).

The tool incorporates variables for age, vital signs, whether the patient was transported by emergency medical service, use of metolazone at home, the presence of cancer, and laboratory data to assess risk. Each variable has a numeric value that is further adjusted by formulae and summed to result in a final numeric score. A range of scores is then used to define 5 distinct categories of mortality risk.

The tool has notably only been assessed for its ability to predict mortality risk. Both the 7- and 30-day respective mortality rates are reported for each of the 5 categories of risk which are as follows: Category 1, 0.0%/0.0%; Category 2, 0.0%/1.9%; Category 3, 0.6%/3.9%; Category 4, 1.9%/5.9%, and Category 5, 3.9%/14.3%. The study did show that physician gestalt generally overestimates the mortality risk of lower-risk patients and underestimates the mortality risk of the highest-risk patients. For this reason, clinicians may use the tool to help prevent the disposition to home of the higher-risk patients for death. However, patients assessed to be at lower risk may still not be confidently discharged home because the tool did not evaluate other important outcomes beyond mortality, such as acute myocardial infarction, need for cardiac intervention, need for endotracheal intubation/mechanical ventilation, need for hemodialysis, and readmission. Additionally, this study was limited by the fact

that the tool was only validated internally. Given the unintuitive calculations that must be further performed for several of the tool's variables, it would be challenging to attempt to calculate a score using this tool in a busy ED without being connected to an online EHMRG7 calculator.

Summary

To date, no study has derived an AHFS risk tool that has been used to prospectively determine an ED patient's disposition. Additionally, no study to date has established the treatment effect of hospitalization on the subsequent outcomes of AHFS patients admitted to the hospital. Given the diverse and complex nature of ED patients with AHFS, there may never be a tool that is sufficiently accurate in assessing the risk that it may be used alone. Instead, we may, more likely, have tools that perform relatively well, and then clinicians must employ shared decision-making strategies to determine what is best for the patient. Still, questions remain as to what outcomes should be considered "meaningful" and what incidence of those outcomes is too high. One would think that the risk tolerance for death may be far less than the risk tolerance for readmission. Should all these outcomes of different significance be grouped together and reported as one event when any of them occur, or should each outcome also be reported separately with their own statistics?

Future Research

Future research should focus on developing an AHFS risk stratification tool that successfully predicts clinically important outcomes and may be easily applied in a prospective, systematic fashion to all ED patients presenting with AHFS. Study patients would then be admitted or discharged solely on the basis of either the tool's risk stratification alone or a reproducible process that incorporates the tool's results and is followed over time for clinically important outcomes. If no AHFS risk stratification tool alone is found to be sufficient in identifying low-risk patients who may be safe for discharge directly home from the ED, then studies should be considered that incorporate shared decision-making. Additional studies that further assess which outcomes are most meaningful, what incidence of these outcomes should be considered unacceptable, and how much admission to a hospital actually prevents adverse outcomes from occurring or being associated with greater morbidity or mortality would also be of value. Finally, the incorporation of prospectively validated risk modeling into formal machine learning algorithms that provide clinical decision support

within existing workflows may not only prove more accurate but also more efficient.[37]

Relevant industry relationships: There were no relevant industry relationships disclosed by the subcommittee members for this topic.

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

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APPENDIX A.

Appendix E1. Literature classification schema.*

Design/Class	Therapy[†]	Diagnosis[‡]	Prognosis[§]
1	Randomized, controlled trial or meta-analysis of randomized trials	Prospective cohort using a criterion standard or meta-analysis of prospective studies	Population prospective cohort or meta-analysis of prospective studies
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series	Case series	Case series

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

Appendix E2. 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

Appendix E3. Likelihood ratios and number needed to treat.*

LR (+)	LR (−)	
1.0	1.0	Does not change pretest probability
1–5	0.5–1	Minimally changes pretest probability
10	0.1	May be diagnostic if the result is concordant with pretest probability
20	0.05	Usually diagnostic
100	0.01	Almost always diagnostic even in the setting of low or high pretest probability

LR, likelihood ratio.
*Number needed to treat (NNT): number of patients who need to be treated to achieve 1 additional good outcome; NNT=1/absolute risk reduction×100, where absolute risk reduction is the risk difference between 2 event rates (ie, experimental and control groups).

APPENDIX E4. PRISMA[5] FLOW DIAGRAMS.

Critical Question 2 Flow Diagram

Identification

Records identified from:
Databases (n = 583)
Other Sources (n = 1)

Duplicate records removed
(n =199)

Screening

Abstracts screened
(n = 385)

Records excluded
(n = 339)

Full-text records screened
(n = 46)

Records excluded
(n = 35)

Records assessed for eligibility
(n = 11)

Records identified with fatal
flaws or ultimately
determined to not be
applicable to the critical
question
(n = 10)

Included

Studies included in review
(n = 1)

Critical Question 3 Flow Diagram

Identification

Records identified from:
Databases (n = 177)
Other Sources (n = 0)

→ Duplicate records removed (n =46)

Screening

Abstracts screened (n = 131)

→ Records excluded (n = 90)

Full-text records screened (n = 41)

→ Records excluded (n = 26)

Records assessed for eligibility (n = 15)

→ Records identified with fatal flaws or ultimately determined to not be applicable to the critical question (n = 14)

Included

Studies included in review (n = 1)

Critical Question 4 Flow Diagram

Identification

Records identified from:
Databases (n = 938)
Other Sources (n = 0)

→ Duplicate records removed (n =426)

Screening

Abstracts screened (n = 512)

→ Records excluded (n = 417)

Full-text records screened (n = 95)

→ Records excluded (n = 81)

Records assessed for eligibility (n = 14)

→ Records identified with fatal flaws or ultimately determined to not be applicable to the critical question (n = 10)

Included

Studies included in review (n = 4)

APPENDIX E5. EVIDENTIARY TABLE

Evidentiary Table.

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
McGivery et al[10] (2018)	II for Q1	Systematic review and meta-analysis	Prospective studies that reported on the sensitivity and specificity of B-lines in dyspneic ED patients; all included studies used at least one of the following alternate tests in their clinical diagnosis: CXR, BNP, NT-pro-BNP, or echocardiography; importantly, data from these tests were blinded from the sonographers; the bedside ultrasound was performed by emergency physicians, emergency medicine residents, ultrasound fellows, medical students, and cardiologists; all studies meeting the inclusion criteria also met the requirements for methodological quality using the CASP questionnaire	3,674 articles identified with 7 ultimately included; N=1,861; the random effects pooled results for sensitivity and specificity for ED-performed bedside LUS for the diagnosis of ADHF were 82.5% (95% CI 66.4% to 91.8%) and 83.6% (95% CI 72.4% to 90.8%), respectively; positive LR was 4.8 (95% CI 2.6 to 9.1), negative LR was 0.19 (95% CI 0.09 to 0.39)	Significant heterogeneity among included studies with large variation in study sample size
Martindale et al[11] (2016)	III for Q1	Systematic review and meta-analysis of both prospective and retrospective studies	Included both prospective and retrospective observational studies; structured searches using MeSH; used QUADAS-2 to assess quality; outcome: AHF	9,405 articles identified with 57 ultimately included; N=17,893; significant study heterogeneity, including prevalence of AHF; LUS showed pooled positive LR for AHF of 7.4	Authors pooled results although significant heterogeneity

Evidentiary Table. (continued)

Staub et al[12] (2019)	III for Q1	Systematic review and meta-analysis	Included both prospective and retrospective observational studies; structured searches using MeSH; used QUADAS-2 to assess quality; outcome: AHF	11,017 articles identified with 14 ultimately included related to AHF; N=2,778; AUROC 91%; sensitivities ranged from 73% to 93%, specificities ranged from 84% to 93%; positive LR ranged from 4.8 to 14, negative LR ranged from 0.07 to 0.54	Significant study heterogeneity
Lian et al[13] (2018)	III for Q1	Systematic review and meta-analysis	Included both prospective and retrospective observational studies; structured searches using MeSH; used QUADAS-2 to assess quality; outcome: AHF	8,033 articles identified in search with 15 ultimately included; N=3,309 patients; significant heterogeneity among findings; pooled sensitivity 85%; range across studies: 33% to 100%; pooled specificity 91%; range across studies: 54% to 100%; positive LR 8.9, negative LR 0.14	Most included studies were deemed low risk of bias, although details of this assessment are sparse; authors pooled results although significant heterogeneity
Pivetta et al[15] (2019)	III for Q1	Randomized clinical trial; 2 emergency departments	Included adult ED patients 18 years of age or older with acute dyspnea, stratified by presumptive etiology (AHF or non-AHF); participants were then randomized to either LUS or CXR/NT-proBNP; outcome: AHF as independently assessed by 2 physicians blinded to allocation	N=518; AUROC for LUS 0.95, AUROC for CXR/NT-proBNP 0.87, AUROC for clinical evaluation along 0.85	Limited generalizability due to 2 sites and LUS performed by specified study emergency physicians

Evidentiary Table. (continued)

Pivetta et al[14] (2015)	III for Q1	Prospective observational study; multiple centers in Italy	Included adult patients 18 years of age or older who presented to the ED with acute dyspnea; emergency physicians assessed clinical diagnosis of AHF and performed LUS; outcomes: AHF as determined by independent review of medical record by 2 physicians blinded to US results	N=1,005; LUS sensitivity 97% (95% CI 95% to 98%), LUS specificity 97% (95% CI 96% to 99%]); initial clinical workup without US sensitivity 85% (95% CI 82% to 88%) and specificity, 90% (95% CI 87% to 92%); CXR alone sensitivity 70% (95% CI 65% to 74%) and specificity 82% (95% CI 79% to 85%)	Large multi-center cohort; possible selection bias; emergency physicians had specific training, so possibly not generalizable to broad emergency care practice
Sartini et al[16] (2017)	III for Q1	Prospective observational study; 1 hospital	Included adult ED patients 18 years of age or older presenting with acute dyspnea not related to trauma; LUS performed by dedicated study-specific emergency physicians; outcome: AHF as determined by an independent panel of experts, including cardiology and emergency medicine	N=236; 48% with AHF LUS Sensitivity 58% Specificity 88% CXR Sensitivity 75% Specificity 86% NT-proBNP Sensitivity 98% Specificity 28%	Limited generalizability due to small sample size and single institution; possible spectrum bias
Nakornchai et al[17] (2019)	III for Q1	Prospective observational study; single center, large urban, tertiary care center in Thailand	Included adult patients 18 year of age or older with acute dyspnea and with AHF as part of the differential; emergency medicine resident blinded to patient information performed US; outcome: AHF as determined by 2 emergency physicians blinded to the US results	N=62; 65% were diagnosed with AHF; sensitivity 60%, specificity 73%	Small sample size; limited generalizability; possible selection bias

Evidentiary Table. (continued)

Buessler et al[18] (2020)	III for Q1	Prospective, multi-center observational study	Patients 50 years of age or older who were admitted for acute dyspnea and for whom the physician had diagnostic uncertainty; excluded patients who experienced trauma or who had systolic BP <70 mm Hg; 4-point, 6-, 8-, and 28-point LUS was performed by ultrasound-certified emergency physicians, as well as clinical assessment using the BREST score; outcomes: final AHF diagnosis at discharge, adjudicated by 2 physicians and blinded to US results	N=117; N=69 with AHF; among the 69 patients the 4-, 6-, 8-, and 28-point LUS identified AHF in 27%, 56%, 55%, and 77% of patients, respectively; C-index was: 73% for the Brest score; 64% for 4-point; 72% for 6-point; 74% for 8-point, and; 72% for 28-point, individually C-index for each increased from 3.5 to 7.3 when added to BREST score with p-values ranging from 0.1 to 0.004	Potential selection bias; US performed by trained, certified, physicians, which may limit generalizability; small sample although heterogeneous clinical sites
Wong et al[21] (2013)	III for Q2	Secondary analysis of the ADHERE-EM registry, US Centers for Medicare and Medicaid, 2004 to 2005, across 83 hospitals	Patients 65 years of age or older who were hospitalized with a primary or secondary diagnosis of HF; Cox proportional hazard model to assess association of time to treatment with a composite 30-day all-cause mortality or readmission	N=6,971; median time to first IV therapy was 2.3 hours (interquartile range of 1.1 to 4.4); 30-day all-cause mortality or readmission was 27.4%; time to treatment was not associated with increased risk of composite 30-day mortality or re-admission (hazard ratio 1.00 [95% CI 1.0 to 1.0]); every hour delay in treatment was associated with risk of in hospital mortality (adjusted odds ratio 1.01 [95% CI 1.00 to 1.02])	Secondary analysis of an existing dataset; multi-center; selection bias possible given inclusion of only older patients

Evidentiary Table. (continued)

Levy et al[22] (2007)	III for Q3	Prospective quasi-experiment, described as a nonrandomized, open-label study; 2 institutions in Detroit	Adult patients 18 years of age or older with a SBP ≥160 mm Hg or mean arterial blood pressure ≥120 mm Hg; exclusions included noncardiac pulmonary edema, need for immediate intubation, or CPR; initial treatment included nonrebreather mask oxygen, sublingual NTG and furosemide; patients deemed to require IV NTG were approached for inclusion; HD IV NTG included 0.3 to 0.5 mcg/kg/min and titrated to maximum of 400 mcg/min, but with initial bolus of 2,000 mcg with subsequent 2,000 mcg boluses every 3 to 5 min at discretion of treating emergency physician; effectiveness outcome: intubation within 6 hours of treatment; safety outcomes: neurological or cardiovascular complications; secondary outcomes: BiPAP, need for ICU, hospital length of stay, renal dysfunction, 30-day ED recidivism	N=64; N=29 HD NTG; Mean dose of IV NTG 6,500 mcg Intubation HD NTG 14% Non-HD NTG 27% BiPAP HD NTG 7% Non-HD NTG 20% ICU Admission HD NTG 38% Non-HD NTG 80% Symptomatic Hypotension HD NTG 3% Non-HD NTG 0% Cardiac Ischemia by Biomarker HD NTG 17% Non-HD NTG 29%	Small sample size; significant imbalances between study groups; control group data obtained retrospectively; no adjustment for confounding

Evidentiary Table. (continued)

Stiell et al[32] (2017)	II for Q4	Multi-center, prospective cohort study; 6 Canadian EDs	Enrollment included a sample of ED patients >50 years of age presenting with dyspnea due to AHF; outcomes: SAE defined as mortality within 30 days of ED visit, or admission, intubation, acute myocardial infarction, major procedure within 14 days	N=1,100; SAEs occurred in 170 (15.5%); prognostic accuracy of the OHFRS was: OHFRS >1 91.8% sensitivity and 24.9% specificity, and when NT-BNP included, OHFRS >1, 95.8% sensitivity and 13.6% specificity for identifying SAE	Potential for intention bias related to admitted patients who may not have experienced SAE simply because they were admitted; potential for selection bias related to convenience enrollment; not all patients had NT-BNP measurements; use of same EDs that were involved in the development of the OHFRS (see Stiell et al 2013)
Stiell et al[33] (2013)	III for Q4	Multi-center, prospective cohort study; 6 Canadian EDs	Enrollment included a convenience sample of ED patients ≥50 y presenting with dyspnea due to ADHF exacerbation; outcome: SAE defined as mortality of any cause within 30 days of the ED visit, or admission, intubation, acute myocardial infarction, major procedure, or relapse within 14 days of the ED visit	N=559; SAEs occurred in 65 (11.6%) and in only 31 (5.5%) who were not admitted to the hospital; The OHFRS was developed and included 10 characteristics with SAEs ranging from 2.8% for a Score=0, and 89.0% for a Score=9 with good calibration (Hosmer-Lemeshow goodness-of-fit p=0.95) and discrimination (AUROC of 0.75)	Potential for selection bias given convenience sampling; OHFRS only internally validated using bootstrap methods; thus, no external validation performed
Collins et al[34] (2015)	III for Q4	Multi-center, prospective cohort study; 4 EDs in the United States	Enrollment included adult patients presenting to the ED with acute HF using the modified Framingham criteria; outcomes: SAE within 30 days, defined as all-cause mortality, acute coronary syndrome, CPR, mechanical cardiac support, intubation, hemodialysis, or need for percutaneous coronary intervention	N=1,033; adverse event occurred in 126 (12%); The STRATIFY decision tool had moderate discrimination (c statistic 0.68) and good calibration; a score of 5 resulted in a sensitivity of 95% and specificity of 14% for severe adverse event	Potential selection bias given convenience sampling; 63 participants withdrew and 18 were lost to follow-up; the STRATIFY decision tool was only internally validated using bootstrap methods; thus, no external validation was performed

Evidentiary Table. (continued)

Lee et al[35] (2019)	III for Q4	Multi-center, prospective cohort study; 9 Canadian EDs	Enrollment included adult patients presenting to the ED with AHF; outcomes: mortality at 7 days; mortality at 30 days	N=1,983; mortality: 39 (2.0%) at 7 days and 138 (7.0%) at 30 days; compared to physician estimation, Emergency Heart failure Mortality Risk Grade (EHMRG7) had improved discrimination (c statistic 0.81 vs 0.71)	Mortality was the only outcome; thus, other important outcomes not assessed

ADHF, acute decompensated heart failure; *AHF*, acute heart failure; *AHFS*, Acute Heart Failure Syndromes; *AUROC*, area under the receiver operating characteristics; *BiPAP*, bilevel positive airway pressure; *BNP*, B-type natriuretic peptide; *CI*, confidence interval; *CXR*, chest x-ray; *ED*, emergency department; *h*, hour; *HD*, high-dose; *IV*, intravenous; *kg*, kilogram; *LR*, likelihood ratio; *LUS*, lung ultrasound; *mcg*, microgram; *MeSH*, Medical Subject Heading; *mg*, milligram; *min*, minute; *NPV*, negative predictive value; *NTG*, nitroglycerin; *NT-proBNP*, N-terminal pro-B-type natriuretic peptide; *OHFRS*, Ottawa Heart Failure Risk Scale; *PPV*, positive predictive value; *QUADAS-2*, Quality Assessment of Diagnostic Accuracy Studies 2; *SAE*, serious adverse event; *US*, ultrasound; *y*, year.