STUDY PROTOCOL

Effect of a Point-of-Care Ultrasound-Driven vs Standard Diagnostic Pathway on 24-Hour Hospital Stay in Emergency Department Patients with Dyspnea—Protocol for A Randomized Controlled Trial

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Purpose: Point-of-care ultrasound (POCUS) helps emergency department (ED) physicians make prompt and appropriate decisions, but the optimal diagnostic integration and potential clinical benefits remain unclear. We describe the protocol and statistical analysis plan for a randomized controlled trial. The objective is to determine the effect of a POCUS-driven diagnostic pathway in adult dyspneic ED patients on the proportion of patients having a hospital stay of less than 24 hours when compared to the standard diagnostic pathway.

Patients and Methods: This is a multicenter, randomized, investigator-initiated, open-labeled, pragmatic, controlled trial. Adult ED patients with chief complaint dyspnea are eligible. Patients are randomized (1:1) to the POCUS-driven diagnostic pathway or standard diagnostic pathway, with 337 patients in each group. The primary outcome is the proportion of patients having a hospital stay (from ED arrival to hospital discharge) of less than 24 hours. Key secondary outcomes include hospital length-of-stay, 72-hour revisits, and 30-day hospital-free days.

Conclusion: Sparse evidence exists for any clinical benefit from a POCUS-integrated diagnostic pathway. The results from this trial will help clarify the promising signals for POCUS to influence patient care among ED patients with dyspnea.

Keywords: focused lung ultrasound, focused cardiac ultrasound, shortness-of-breath, diagnostic effectiveness

Introduction
Background and Rationale

Acute dyspnea is a dominating chief complaint in emergency departments (ED) worldwide.[1–6] Nevertheless, diagnostic uncertainty is still substantial due to unspecific and overlapping symptom complexes in disorders causing dyspnea, most frequently chronic obstructive pulmonary disease, pneumonia, heart failure, pulmonary embolism, and asthma.[7–11] The evaluation of dyspnea is highly dependent on medical history and physical examination. But despite the additional usage of electrocardiograms, chest x-rays, arterial blood gas analysis, and venous blood sample test panels, expert adjudicators post-discharge still identify 30–40% of dyspneic patients with incorrect presumptive ED diagnoses.[12–15]

Point-of-care ultrasound (POCUS) poses as a potentially valuable examination in the diagnostic work-up of ED patients with dyspnea. The diagnostic accuracy of focused lung and cardiac ultrasound for diagnosing most disorders causing acute dyspnea is excellent.[16–23] However, the clinical benefit and how to optimally integrate it into current diagnostic pathways are still unclear.

For ED patients with dyspnea, no studies have found evidence that a diagnostic pathway guided by POCUS increases survival. However, it seems to lead to more prompt and appropriate decision-making, likely minimizing the patient's disease burden and making the healthcare process more efficient.[12,13,15,24,25] Recent studies have found promising results for shorter hospital admissions.[15,26–28] Based on these results, we hypothesize that a POCUS-driven diagnostic pathway shortens the hospital length of stay for patients admitted to the ED with chief complaint dyspnea.

Objectives

The study's primary objective is to compare the number of patients having a hospital stay of less than 24 hours in the POCUS versus standard care group.

The secondary objectives are to investigate the effect of a POCUS-driven diagnostic pathway on (1) hospital length of stay; (2) use of image resources; (3) 72-hour revisits; (4) 30-day hospital-free days; (5) time to treatment; and (6) patients' experiences.

A diagnostic sub-study is planned a priori (see the Supplemental Material).

Materials and Methods
Protocol

The entire protocol is provided in the Supplemental Material, and all previous versions are available from the trial website.[29] The protocol is developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.[30,31] The trial was registered at ClinicalTrials.gov (Identifier: NCT 05674916 (date: 2023 January 9)). The Committee on Health Research Ethics in the Central Denmark Region approved the trial protocol (Identifier: 1–10-72-160-22 (date: 2022 November 24)). This trial will comply with the Declaration of Helsinki.

A preliminary version of this work was presented at the PHD DAY conference 2023 at Aarhus University, Denmark.[32]

Trial Design

The trial is a multicenter, randomized, investigator-initiated, open-labeled, pragmatic, controlled trial with 1:1 allocation.

Setting

The trial is conducted at EDs in Denmark. A complete list of participating centers is provided in the protocol.

Investigators

Participating physicians were recruited based on the following parameters: 1) certified competence in POCUS 2) an experience of >50 cardiac and lung scans; 3) clinical experience corresponding to three post-graduate years; 4) be in residency training or be specialized; and 5) be working in emergency medicine.

Eligibility Criteria

Patients will be included based on the following inclusion criteria: ED visit, age ≥18 years, chief complaint is dyspnea, and trial physician presence.

Chief complaint dyspnea is defined through one of the following four criteria:

a. Triaged with Dyspnea (or similar, ie, Breathlessness) as the chief complaint in the local ED OR prehospital triaging system (determined by a triaging nurse or emergency medical service (EMS) technician, respectively).
b. Chief complaint is not implemented in local triage system AND prehospital triage not performed, BUT

    i. In the general practitioner referral note, the wording is compatible with chief complaint Dyspnea, according to a predefined systematic word search string (Supplementary Material).

    ii. In the prehospital notification OR EMS crew notes, the wording is compatible with chief complaint Dyspnea, according to a predefined systematic word search-string (Supplementary Material).

    iii. The chapter for Dyspnea (or similar, ie, Breathlessness) is used in the criteria-based EMS dispatch tool.

Exclusion criteria are: Fulfillment of coded rapid-response team criteria (ie, trauma, surgical, or medical emergencies), prior focused lung or focused cardiac ultrasound in the current ED stay, prior enrollment in the trial, unable to consent, and non-Danish-speaking.

Study Flow

Patients will be screened by the trial physician, who will look through lists of patients arriving at the ED. Patients that trial physicians screen but do not include will be documented prospectively with the reason for exclusion in a screening log using the paper Case Report Form (CRF) (Supplementary Material). During the initial assessment, and upon fulfillment of inclusion criteria, the physician will ask for informed consent, enroll, and randomize the patient. The exact time of randomization should be immediately after the consent has been signed.

A diagnostic survey will be filled out twice by the physician during the diagnostic process (Supplementary Material). After hospital discharge, patients will receive an electronic questionnaire concerning their experiences from the ED stay (Figure 1) (Supplementary Material).

Interventions

Standard Diagnostic Pathway

The standard diagnostic pathway will be based on the treating physician's discretion and diagnostic probabilities; it will likely include, but not be limited to, blood samples, blood gases, electrocardiogram, and chest x-ray. Focused lung and cardiac ultrasound cannot be performed while the patients stay in the ED unless clinical deterioration and patient safety demand it. Other POCUS modalities can be applied immediately (eg, lower extremity compression or focused abdominal ultrasound). Chest computed tomography (CT), CT pulmonary angiogram, echocardiography, and other next-line testing remain exclusively at the treating physicians' discretion, guided by national disease-specific guidelines.[33–36]

Point-of-Care Ultrasound-Driven Diagnostic Pathway

Focused lung and cardiac ultrasound will be performed by the treating physician during the primary assessment. The final decision on next-line imaging (ie, chest x-ray, echocardiography, or CT) and further diagnostic testing remain at the treating physicians' discretion and should incorporate history, physical examinations, and POCUS. Per protocol, diagnostic decision recommendations will be provided for the treating physician (Supplementary Material).

POCUS will be performed by the treating ED physician at the discretion of timing, workflow and preference of ultrasound apparatus, transducer, and pre-set; the protocols are in accordance with international standards.[37–39] Focused lung ultrasound will include eight zones (anterior and lateral) and evaluate pneumothorax, B-line pattern, lung consolidation, and pleural effusion (Supplementary Material). Focused cardiac ultrasound will consist of four views (subxiphoid four-chamber view, parasternal long-axis view, parasternal short-axis view, and apical four-chamber view) and evaluate pericardial fluid, right ventricle dilation, and left ventricular systolic contractility (Supplementary Material). Other POCUS modalities can be applied at the physician's discretion (eg, lower extremity compression or focused abdominal ultrasound).

Blinding

Blinding patients or clinical teams will not be attempted.

	STUDY PERIOD						
	Enrolment	Randomization	Post-randomization		Close-out		Follow-up
TIMEPOINT	-t1	0	t1 PA/± POCUS	Ended SDP	ED Discharge	Discharge	30 days
ENROLMENT:							
Eligibility screen	X						
Screening log	X						X
Informed consent		X					
Randomization		X					
INTERVENTIONS:							
POCUS-driven DP			X				
SDP			X				
ASSESSMENTS:							
Case Report Form	X	X					
Diagnostic survey			X	X			
Patient Questionnaire						X	
Retrospective data retrieval (baseline characteristics, vital parameters, biochemical findings, microbiologic findings, treatments, admission metrics [timing and units], readmissions, mortality)						X	X
Manual record review						X	X
(PA findings, ultrasound findings, radiologic findings)							

Figure 1 SPIRIT flow diagram: Schedule of enrolment, interventions, and assessments.
Abbreviations: DP, diagnostic pathway; SDP, standard diagnostic pathway; PA, primary assessment.

Randomization

Patients will be randomized in a 1:1 ratio in blocks with random sizes of 2, 4, or 6 within each site. The randomized sequence of study identification numbers will be generated using the "blockrand" R package.[40,41] Opaque randomization envelopes will be prepared, packed, and shipped to participating centers based on their current tally and inclusion rate by the principal investigator. The allocation sequence list and block sizes are only known by the principal investigator and steering committee statistician.

Outcomes

The primary outcome, 24-hour hospital stay, will be defined as the proportion of patients having a hospital stay (from ED arrival to hospital discharge) of less than 24 hours.

Secondary outcomes

Hospital length-of-stay, defined from ED arrival to hospital discharge, will secondarily be analyzed as a non-binary outcome.

Image resources will be quantified in numbers of the following imaging techniques performed during the current hospital stay: chest x-rays, echocardiography, CT pulmonary angiography, and chest CT.

Seventy-two-hour revisits will be defined as a composite outcome including any unplanned hospital stay within 72 hours from the previous hospital discharge, in-hospital mortality, and mortality within 72 hours from the previous hospital discharge.

Hospital-free days will be defined as the number of days within the 30-day period following hospital discharge where the patient is not hospitalized and alive.[42] In-hospital death will be computed as zero hospital-free days. Registrations showing that a patient has left home for a hospital contact will be computed as 1 day that was not hospital-free (ie, outpatient or paraclinical follow-up visits). Long- or short-stay nursing facilities, inpatient hospice facilities, or rehabilitation facilities will be hospital-free, as will all days at home, including those with home-based medical services.[42]

Time to treatment will be defined as time from ED arrival until administration of any of the following treatment subgroups: antibiotics, diuretics, and anticoagulants. Only ED administrations will be included. Oral and intravenous treatments will not be separated.

Patients' experiences will be defined on a 1–5 Likert scale (from "Not at all" to "Very much") with two alternative responses ("Don't know" and "Not relevant for me").

Sample Size Calculation

Based on a previous study with a similar population, the proportion of patients discharged within 24 hours is expected to be 24%.[15] They found that 40% of POCUS group patients were discharged within 24 hours, corresponding to a risk difference of 16% (24% versus 40%). We regard a risk difference of 10% as clinically relevant. Based on a chi-squared test, assuming 5% dropouts and an alpha of 0.05, a sample size of 674 patients (337 per group) is needed to obtain 80% power.

Statistical Analysis Plan

The statistical analyses will adhere to the Consolidated Standards of Reporting Trials (CONSORT)-guidelines.[43,44] Post-randomization exclusion from analyses will only happen from withdrawal or mislaying of patient consent or duplicate inclusion of the same individual. Apart from that, all analyses will be conducted on an intention-to-treat basis.[45,46] All tests will be two-sided, a p-value <0.05 will be considered significant, and all confidence intervals will have 95% coverage.

The primary outcome will be presented as the absolute number and proportions in each group. Groups will be compared using risk difference and relative risk with 95% confidence intervals, and a p-value will be calculated based on a binary regression.

Hospital length-of-stay will be analyzed using time-to-event analysis and pseudo-observations. The Nelson-Aalen estimator will be applied to estimate the cumulative hazard rates in the intervention and control groups. A Cox regression

will be used to compare the overall hazards. Lastly, a generalized linear model using pseudo-observations accounting for in-hospital mortality as a competing risk will compare between-group discharge risks within 3 and 7 days (including the endpoint day, 72 and 168 hours).

Image resources and 72-hour revisits will be presented as the composite number and incidence proportion and compared by risk difference and relative risk based on a binary regression.

Thirty-day hospital-free days will be presented as raw means in the two groups with 95% confidence intervals. A Tobit regression model will be built upon a logistic model for mortality and linear regression for days alive outside the hospital within 30 days for patients discharged alive. Between-group comparison will be quantified as a mean difference from the Tobit regression.

Time to treatment will be presented as a composite outcome with a median and interquartile interval for both groups. Comparison will be performed using Cox regression analysis.

Patients' experiences will be treated continuously, comparing mean scores between groups using an unpaired t-test. For descriptive comparison, category distributions will be depicted by group.

Subgroup analyses will be performed on the relative scale for the primary outcome, according to: (1) ED arrival (day, evening, or night); (2) weekdays or weekends/holidays; (3) physicians' ultrasound competence categorized; (4) physicians' post-graduate years categorized; (5) prehospital presumptive diagnosis; and (6) 10-year patient-age intervals.

Data Collection and Data Management

The case report form (CRF) will be available in paper and electronic format. The paper-CRF will be filled and stored during all prospective screenings of non-included patients. The electronic CRF (eCRF) will be filled out for all included patients.

Baseline characteristics, vital parameters, biochemical and microbiologic results, treatments, admission metrics (timing and departments), readmissions, and mortality will be collected retrospectively using routinely collected patient-record data. All data will be collected longitudinally using the personal identification number as the key identifier. The primary physical assessment, ultrasound, and radiologic findings will be manually entered and coded into a REDCap® database based on a review of medical records.

To minimize missing data, e-mail and SMS reminders of the diagnostic survey will be sent to treating physicians at four, six, and eight hours post-randomization.

Trial physicians will additionally fill out a survey regarding their experience, including post-graduate years, specialization, ultrasound certification, and years of using ultrasound (Supplementary Material).

All data will be kept in a secure content management system (Hyland Alfresco™, Boston, Massachusetts, USA). Data management will be done using STATA®.[47] Ultrasound film clips will be stored securely, according to local legal regulations.

Data handling will comply with the General Data Protection Regulation (European Union 2016/679) and the Danish Act for Data Protection (ACT 502 of 23rd May 2018).

Ethical Considerations and Consent

Consent is obtained according to Danish law.

Data Sharing

Six months after the publication of the last results, all de-identified individual patient data will be made available for data sharing.[48] Procedures, including re-coding of critical variables, will be put in place to allow for complete de-identification of the data. Data will be completely anonymized according to Danish law.

Discussion

The current article describes the design of the POCUS PATHWAY trial, which tests the effect of a POCUS-driven diagnostic pathway in adult dyspneic ED patients on the proportion of patients having a hospital stay of less than 24 hours when compared to the standard diagnostic pathway.

Increasing costs, crowding, and elderly burden call for healthcare systems to provide simplifications. For that matter, in ED patients with dyspnea, POCUS holds a potential that is still not fully elucidated.

The outcomes addressed in this trial will cover important interests of patients and organizations.[49] We believe length-of-stay as the primary outcome is meaningful if it does not compromise 72-hour revisits and 30-day hospital-free days. Together, these results will help clarify the promising signals for POCUS to influence patient care.

Status

The trial started on the 25th of January 2023. To date, 490 patients have been included (1.3 per day). Assuming a similar inclusion rate, inclusion is expected to be finalized by July 2024. The primary results will be reported after 30 days of follow-up and are anticipated in late 2024.

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Disclosure

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