Circulation

ORIGINAL RESEARCH ARTICLE

A Randomized Controlled Trial of Thoracentesis in Acute Heart Failure

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BACKGROUND: TAP-IT (Thoracentesis to Alleviate Cardiac Pleural Effusion–Interventional Trial) investigated the effect of therapeutic thoracentesis in addition to standard medical therapy in patients with acute heart failure and sizeable pleural effusion.

METHODS: This multicenter, unblinded, randomized controlled trial, conducted between August 31, 2021, and March 22, 2024, included patients with acute heart failure, left ventricular ejection fraction ≤45%, and non-negligible pleural effusion. Patients with very large effusions (more than two-thirds of the hemithorax) were excluded. Participants were randomly assigned 1:1 to upfront ultrasound-guided pleural pigtail catheter thoracentesis in addition to standard medical therapy or standard medical therapy alone. The primary outcome was days alive out of the hospital over the following 90 days; key secondary outcomes included length of admission and 90-day all-cause mortality. All outcomes were analyzed according to the intention-to-treat principle.

RESULTS: A total of 135 patients (median age, 81 years [25th; 75th percentile, 75; 83]; 33% female; median left ventricular ejection fraction, 25% [25th; 75th percentile, 20%; 35%]) were randomized to either thoracentesis (n=68) or standard medical therapy (n=67). The thoracentesis group had a median of 84 days (77; 86) alive out of the hospital over the following 90 days compared with 82 days (73; 86) in the control group (*P*=0.42). The mortality rate was 13% in both groups, with no difference in survival probability (*P*=0.90). There were no differences in the duration of the index admission (control group median, 5 days [3; 8]; thoracentesis group median, 5 days [3; 7], *P*=0.69). Major complications occurred in 1% of thoracenteses performed during the study period.

CONCLUSIONS: For patients with acute heart failure and pleural effusion, a strategy of upfront routine thoracentesis in addition to standard medical therapy did not increase days alive out of the hospital for 90 days, all-cause mortality, or duration of index admission. The current findings lay the groundwork for future research to confirm the results.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT05017753.

Key Words: heart failure ■ pleural effusion ■ thoracentesis

Pleural effusion is present in more than half of patients admitted to the hospital with acute decompensated heart failure.[1–3] For ≈20% of patients, the effusion occupies more than one-third of the hemithorax.[4,5] Invasive drainage by therapeutic thoracentesis may be used to relieve shortness of breath for patients with

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Clinical Perspective

What Is New?

- TAP-IT (Thoracentesis to Alleviate Cardiac Pleural Effusion–Interventional Trial) is the first randomized controlled trial to investigate the effectiveness of upfront therapeutic thoracentesis in addition to standard medical therapy compared with medical therapy alone in patients admitted to the hospital with acute heart failure and pleural effusion.
- A strategy of referring to upfront therapeutic thoracentesis did not increase the number of days alive out of the hospital over the following 90 days, survival probability, or patient-reported quality of life, and did not reduce the duration of the index admission.

What Are the Clinical Implications?

- In patients with acute heart failure, left ventricular ejection fraction ≤45%, and sizable pleural effusion (amenable for thoracentesis but less than two-thirds of the hemithorax), reducing filling pressures with diuretics and guideline-directed medical therapy should be the primary treatment target, because the addition of therapeutic thoracentesis does not contribute to a shorter duration of admission or a more favorable prognosis in the following 90 days.
- Routine referral to upfront therapeutic thoracentesis is not recommended, but can be considered on an individual basis after carefully considering potential complications.

Nonstandard Abbreviations and Acronyms

CONSORT	Consolidated Standards of Reporting Trials
DAOH	days alive out of the hospital
eGFR	estimated glomerular filtration rate
GDMT	guideline-directed medical therapy
KCCQ	23-item Kansas City Cardiomyopathy Questionnaire
LVEF	left ventricular ejection fraction
NT-proBNP	N-terminal pro–B-type natriuretic peptide
RCT	randomized controlled trial
TAP-IT	Thoracentesis to Alleviate Cardiac Pleural Effusion–Interventional Trial

sizeable effusions.[6] Thoracentesis provides immediate symptom relief but poses a risk of complications.[7–9] No evidence exists from randomized controlled trials (RCTs) investigating thoracentesis in pleural effusion related to heart failure. Therefore, treatment guidelines do not provide recommendations regarding the indications for or timing of thoracentesis.[10,11] Thoracentesis is performed at increasing rates, and there is a need for evidence of the effects of thoracentesis in pleural effusion related to heart failure.[12] TAP-IT (Thoracentesis to Alleviate Cardiac Pleural Effusion–Interventional Trial) investigated the effectiveness of upfront thoracentesis in addition to standard medical therapy compared with medical treatment alone on patient-relevant outcomes in patients admitted to the hospital with acute heart failure and pleural effusion.

METHODS

Study Design

TAP-IT was a pragmatic, unblinded, multicenter RCT (URL: https://www.clinicaltrials.gov; Unique identifier: NCT05017753). A detailed description of the rationale and trial design has been published previously.[13] The study was approved by the capital region of Denmark scientific ethical committee (approval H-20060817). Participants were recruited and enrolled by physicians specialized in heart failure at 10 cardiology departments at academic hospitals across Denmark, including 3 tertiary heart centers. All participants provided written informed consent. The data supporting the findings of this study are available from the corresponding author upon reasonable request. This report adheres to the CONSORT guidelines (Consolidated Standards of Reporting Trials) with details provided in the Supplemental CONSORT checklist.

Participants

Adult patients (≥18 years of age) admitted to the hospital with signs and symptoms of acute heart failure were eligible for inclusion if they had a left ventricular ejection fraction (LVEF) ≤45% and a non-negligible pleural effusion related to heart failure. No specific quantitative measure of the effusion was required, but the effusion had to be sizable enough for the physician to find drainage by thoracentesis clinically relevant and feasible. A strict definition of size or quantity was not applied because incorporating a quantitative assessment of pleural effusion did not mirror clinical practice at the participating hospitals. Patients were deemed suitable for thoracentesis by the treating physician on the basis of the appearance of the pleural effusion on images available in the clinical setting. Thus, the resulting population reflects patients considered appropriate for thoracentesis based on current clinical practice. Patients with new-onset heart failure and patients with acute decompensated chronic heart failure were eligible. A high likelihood of heart failure as the pathogenesis of the effusion was intended. Hence, patients with an LVEF >45% were not considered for the trial; we considered that pleural effusion in patients with normal ejection fraction was more likely to possibly represent noncardiac pathogeneses. Patients were excluded if one of the following criteria was met: indication for diagnostic thoracentesis, contraindication to thoracentesis, severely impaired hemodynamics or respiratory failure, massive effusion occupying more than two-thirds of the hemithorax, pulmonary or pleural infections, an intrathoracic procedure within 3 months (including thoracentesis), severe aortic stenosis, estimated glomerular filtration rate (eGFR) <15 mL·min·1.73 m^2, or dialysis.

In addition, patients with a planned or expected admission >10 days for conditions other than heart failure were excluded. A detailed description of the eligibility criteria is available in Table S1 and has been reported previously.[13]

Randomization and Blinding

All participants who provided written informed consent were randomly allocated 1:1 to either the thoracentesis group or the control group. The randomization sequence was generated by Internet-based randomization software stratified according to the status of anticoagulant therapy and enrolling site with permuted blocks and block sizes ranging from 2 to 4 patients. Neither the participants, the treating physicians, nor the investigators were blinded to treatment allocation.

Intervention, Comparator, and Follow-Up

The control group received standard medical therapy, with the treating physician determining the dose of diuretics and guideline-directed medical therapy (GDMT). The thoracentesis group was referred to upfront thoracentesis in addition to standard medical therapy. Thoracentesis was performed according to local practices, including any required interruption of anticoagulant therapy. The standard procedure was ultrasound-guided insertion of an intercostal small-bore pigtail catheter, usually 5-8 French, and passive drainage over a few hours. In patients with bilateral non-negligible pleural effusion, bilateral thoracentesis could be performed at the discretion of the treating physician. To ensure the safety of the participants in the control group, thoracentesis was allowed in patients who developed an indication for diagnostic thoracentesis or whose condition deteriorated to a state during which an exclusion criterion was fulfilled. Participants in the control group with diuretic-resistant pleural effusion with no response to pharmacological therapy by day 5 could be referred to thoracentesis. Clinical examination, laboratory testing, and imaging, including echocardiography during the index admission, were performed according to the standard of care of each department, and participants were discharged when deemed appropriate by the treating physician. There were no trial-related follow-up visits. During the 90-day follow-up period, participants were contacted on day 14 after discharge to arrange questionnaire follow-up by telephone, mail, or email, depending on participant preference. On day 14 after discharge, participants were given the 23-item Kansas City Cardiomyopathy Questionnaire (KCCQ) and selected questions from the Questions About Acute Hospitalisation survey used in the annual Danish National Survey of Patient Experiences.[14] The KCCQ was repeated on day 90. All other baseline and outcome data were collected from the participants' electronic health records and managed using REDCap electronic data capture tools hosted at the Capital Region of Denmark.[15]

Outcomes

The primary outcome was the number of days alive out of the hospital (DAOH) in the 90 days after randomization. Hospitalization was defined as lasting across a change in calendar date. Key secondary outcomes were index admission length, all-cause mortality, and time to first all-cause hospitalization or all-cause death. The number of days alive and not hospitalized because of heart failure during 90 days was added as a secondary outcome after the trial commenced. Heart failure–related hospitalization was defined according to the recommendations from the Standardized Data Collection for Cardiovascular Trials Initiative.[16] Patient-reported secondary outcomes were quality of life measured by the KCCQ overall summary score on days 14 and 90 and each participant's overall satisfaction with the treatment and care during the index admission. Key safety outcomes were the number of severe and common complications of thoracentesis, including thromboembolic events within 30 days, because anticoagulant therapy for some participants was paused before thoracentesis.

Statistical Analysis

A sample of 126 participants was required to detect a difference of 3 days in the primary outcome with an α of 0.05 and 90% power. This was based on the assumption that participants referred to thoracentesis in addition to medical therapy would have a mean of 85 DAOH in 90 days compared with a mean of 82 days in the control group receiving only medical therapy, with a standard deviation of 5 days and 5% in-hospital mortality in both groups.[17–19]

Analyses were prespecified in a statistical analysis plan (available at URL: https://www.clinicaltrials.gov; Unique identifier: NCT05017753) before the last patient was included and performed according to the intention-to-treat principal. The data required for the primary outcome analysis were complete. During the trial, we became aware that the primary outcome measure was likely to follow a significantly non-normal distribution.[20] Therefore, in the statistical analysis plan, the main analysis for between-group comparison was prespecified as the Wilcoxon-Mann-Whitney test with the Mann-Whitney parameter as effect estimate with a 95% CI interpreted under the proportional odds assumption.[21] The Mann-Whitney parameter is the probability that a random individual in the intervention group has more DAOH than a random individual in the control group. Thus, an estimate of 0.5 is equivalent to no difference between the groups. To assess the robustness of the main analysis, we performed a sensitivity analysis with Wilcoxon-Mann-Whitney tests stratified by site and anticoagulant therapy. Secondary outcomes were compared using the Student *t* test, Welch *t* test, Wilcoxon-Mann-Whitney test, χ^2 test, or Fisher exact test, as appropriate. Time-to-event analysis estimated by the Kaplan-Meier method was compared using the log-rank test. The main analyses of patient-reported outcomes were complete-case analyses of overall patient satisfaction and KCCQ overall summary scores at days 14 and 90. Partial nonresponders on the KCCQ were handled according to the scoring instructions provided by the developer and licensor.[14] Data are reported as median (25th; 75th percentile) or mean±SD for continuous variables depending on distribution and number (%) for categorical variables. Statistical significance was defined as a 2-sided *P* value <0.05. All analyses were performed using R version 4.4.1 (R Foundation for Statistical Computing).[22]

RESULTS

Population

Between August 31, 2021, and December 22, 2023, we assessed 255 patients for eligibility, and 136 were

randomly assigned to the thoracentesis (n=69 [51%]) or control group (n=67 [49%]; Figure 1). The investigators retracted 1 participant allocated to the intervention group from the study shortly after randomization because the informed consent was deemed invalid. This resulted in a total study population of 135 participants: 68 (50%) in the thoracentesis group and 67 (50%) in the control group. The last participant completed the 90-day follow-up on March 22, 2024. The groups were comparable across baseline characteristics (Table 1). Participants had a median of 81 years of age (75; 84) and 33% were women. Participants had symptoms and signs of decompensated heart failure, a median LVEF of 25% (20; 35) and a median NT-proBNP (N-terminal pro–B-type natriuretic peptide) level of 5899 pg/mL (3649; 10 997). Overall, 53% (n=72) presented with new-onset heart failure, and 49% (n=66) received anticoagulation therapy. Participants were randomized at a median of 21 hours (14; 35) after admission. Most participants had multiple images by different modalities performed as part of their diagnostic workup before randomization. Computed tomographic scan results were available in 30 (22%), ultrasound results in 62 (46%), and chest X-rays were performed in 113 (84%). Pleural effusion was bilateral in 73% (n=99).

Intervention

In the intention-to-treat population, the median time from randomization to thoracentesis (n=59) was 22 hours (3; 31; minimum 0 to maximum 97 hours). The subgroup of 29 participants who received anticoagu-

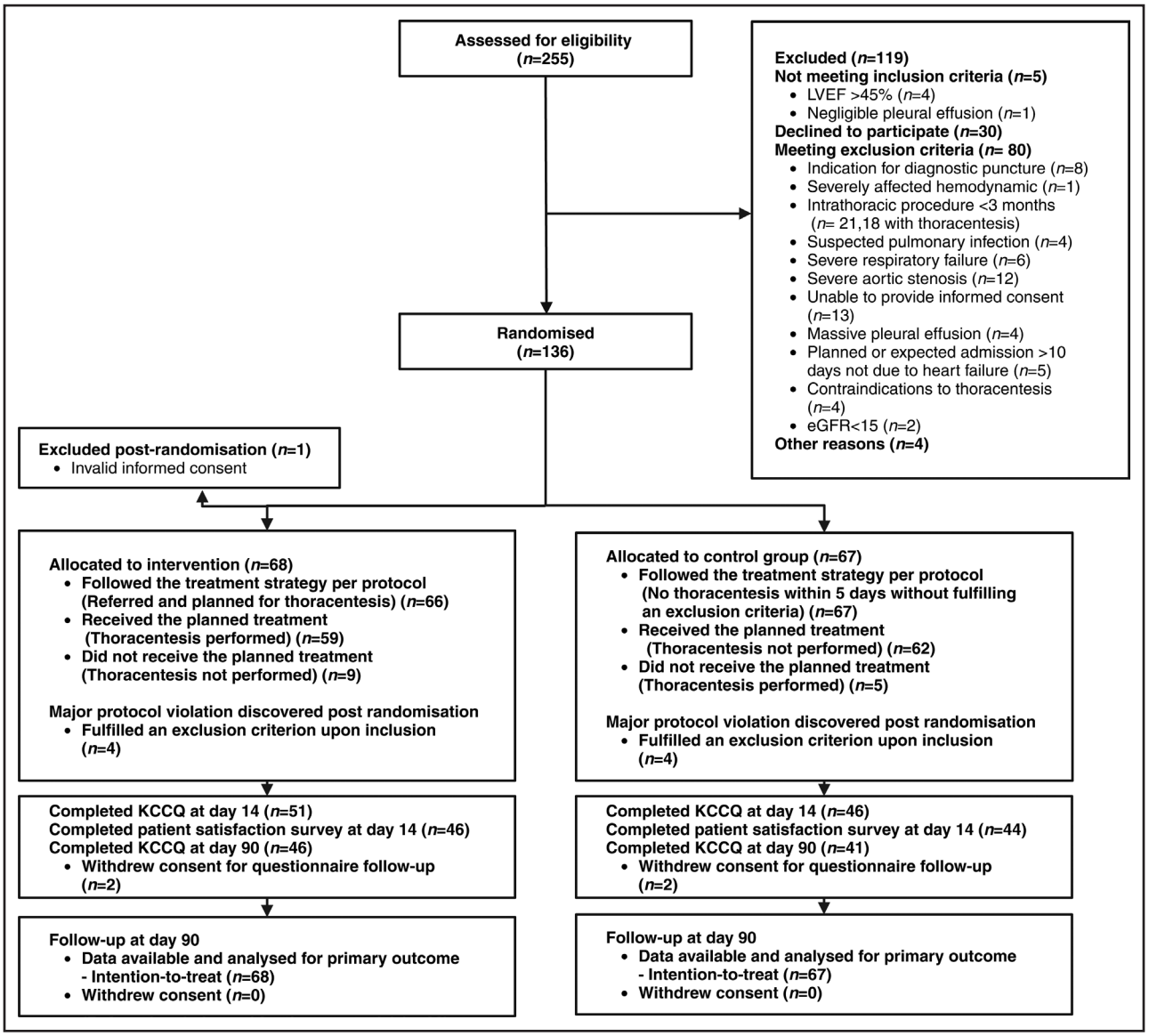

Figure 1. CONSORT diagram of patient flow.
CONSORT indicates Consolidated Standards of Reporting Trials; eGFR, estimated glomerular filtration rate; KCCQ, 23-item Kansas City Cardiomyopathy Questionnaire; and LVEF, left ventricular ejection fraction. Created with BioRender.com.

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Table 1. Baseline Characteristics

Characteristics	Control group (n=67)	Thoracentesis group (n=68)
Demographic		
Age, y	82 (76; 87)	80 (73; 84)
Female sex	25 (37)	20 (29)
White race	67 (100)	68 (100)
Included at tertiary heart center	13 (19)	14 (21)
Clinical		
Body mass index, kg/m^2	26.0±6.4	26.7±6.0
Rales or attenuation on auscultation	56 (84)	49 (72)
Location of pleural effusion		
Right	11 (16)	14 (21)
Left	6 (9)	5 (7)
Bilateral	50 (75)	49 (72)
Dyspnea	67 (100)	68 (100)
Peripheral edema	52 (78)	55 (81)
Orthopnea	32 (48)	32 (47)
Ascites	6 (9)	12 (18)
Fatigue	19 (28)	17 (25)
CSHA Clinical Frailty Scale group		
Not frail (score 1–3)	22 (33)	30 (44)
Vulnerable (score 4)	15 (22)	17 (25)
Frail (score 5–7)	30 (45)	21 (31)
Heart failure		
New onset	38 (57)	34 (50)
Months since diagnosis	0.1 (0.0; 70.4)	0.9 (0.0; 52.4)
New York Heart Association class		
2	1 (2)	2 (3)
3	29 (43)	27 (40)
4	37 (55)	39 (57)
Left ventricular ejection fraction, %	25 (20; 35)	25 (15; 35)
Ischemic etiology	28 (42)	27 (40)
Cardiac resynchronization therapy	6 (9)	7 (10)
Implantable cardioverter defibrillator	6 (9)	14 (21)
Cardiovascular comorbidities		
Hypertension	42 (63)	43 (63)
Atrial fibrillation or flutter	38 (57)	37 (54)
Other comorbidities and risk factors		
Chronic obstructive pulmonary disease	14 (21)	13 (19)
Diabetes	16 (24)	21 (31)
Chronic kidney disease	16 (24)	19 (28)
Known liver disease	1 (2)	1 (2)
Active or former smoker	36 (54)	39 (57)
Known alcohol use >7/14 units/wk (women/men)	11 (16)	15 (22)
Laboratory values		
Hemoglobin, mmol/L	7.8±1.4	8.1±1.3
Sodium, mmol/L	139±5	139±5
Potassium, mmol/L	3.8±0.5	3.7±0.5
Creatinine, µmol/L	108 (81; 141)	101 (76; 142)
eGFR, mL·min·1.73 m^2	56±21	62±26
NT-proBNP, pg/mL	5958 (3909; 11 118)	5463 (2941; 10 360)
Albumin, g/L	32.0±5.1	31.5±3.5
Troponin T/I above upper reference level	40 (63)	37 (56)
C-reactive protein, mg/L	11 (4; 30)	13 (5; 29)
Medication		
ACEI/ARB/ARNI	37 (55)	34 (50)
Beta-blocker	27 (40)	30 (44)
Mineralocorticoid receptor antagonist	9 (13)	16 (24)
Sodium-glucose cotransporter 2 inhibitor	10 (15)	11 (16)
Taking loop diuretics by the time of admission	25 (37)	20 (29)
Furosemide-equivalent preadmission dose in the subgroup receiving loop diuretics, mg/d	80 (40; 120)	80 (40; 120)
Anticoagulant therapy	32 (48)	34 (50)

Values are given as median (25th; 75th percentile), n (%), or mean±SD. ACEI/ARB/ARNI indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor–neprilysin inhibitor; CSHA, Canadian Study of Health and Aging; eGFR, estimated glomerular filtration rate; and NT-proBNP, N-terminal pro–B-type natriuretic peptide.

lant therapy waited a median of 30 hours (22; 48) before the procedure. By thoracentesis, a median of 1062 mL pleural effusion (700; 1744; minimum 150 to maximum 6200 mL) was drained, and 68% of the intervention group (46 out of 68) had >500 mL drained. In the thoracentesis group, 2 participants were not referred and planned for thoracentesis and were classified as crossovers according to the study protocol and statistical analysis plan. In adherence with the protocol, 7 participants (10%) in the thoracentesis group did not undergo the procedure because the performing physician did not find an effusion large enough for safe catheter placement. This group waited a median of 48 hours (32; 59); only 3 were on anticoagulant therapy. Five participants (8%) in the control group underwent thoracentesis (one had 2 procedures attributable to complications) during the index admission because they developed an indication for a diagnostic puncture, experienced clinical deterioration, or had an insufficient treatment response after 5 days. All were in adherence to the protocol. This ultimately resulted in an as-treated population of 64 participants (47%) having thoracentesis performed and 71 (53%) treated with standard pharmacological therapy only during the index admission (Figure 1). Detailed descriptions of the indications or reasons for refraining from thoracentesis are listed in Table S2.

Primary Outcome

There was no difference in the primary outcome between the 2 groups (Mann-Whitney parameter, 0.54 [95% CI, 0.44–0.63]; *P*=0.42). In the thoracentesis group, the median number of DAOH during the 90 days after randomization was 84 (77; 86), compared with 82 (73; 86) in the control group (Figure 2). The results were robust in sensitivity analysis with stratification by site or treatment status for anticoagulant therapy (Table S3) and similar in the as-treated population (Table S4).

Key Secondary Outcomes

The median duration of the index admission was 5 days in both groups (control group, 5 days [3; 8]; thoracentesis group, 5 days [3; 7]; Mann-Whitney parameter, 0.48 [95% CI, 0.39–0.58]; *P*=0.69; Table 2). The 90-day all-cause mortality rate was 13% (9 patients in each group), with an in-hospital mortality rate of 3% (2 patients in each group) and no difference in survival probability between the 2 groups (*P*=0.90; Table 2 and Figure 3A). In the thoracentesis group, 28 patients (41%) experienced all-cause hospitalization during the following 90 days compared with 28 (42%) in the control group (*P*=0.99), and the cumulative risk of first all-cause hospitalization or all-cause death was similar in the groups (*P*>0.99; Figure 3B). The median number of days alive and not hospitalized because of heart failure was also similar between the groups (thoracentesis group, 85 [84; 87]; control group, 84 [80; 86]; Mann-Whitney parameter, 0.57 [95% CI 0.47–0.66]; *P*=0.16).

Results across the primary and main secondary outcomes were similar in the as-treated population (Table S4; Figure S1) and the prespecified subgroup of participants with and without anticoagulant therapy (Table S5). Similar results were found in post hoc subgroup analysis in participants with acutely decompensated chronic heart failure or new-onset heart failure (Table S6) and in participants classified as having large pleural effusion (n=76 [56%]) or a small or medium pleural effusion (n=54 [40%]) based on a semiquantitative evaluation (Table S7).[23]

Patient-Reported Outcomes

On day 14, 72% of participants (97 out of 135) completed the questionnaires, with no difference in response rate between the 2 groups (*P*=0.53). Five participants (4%) died before day 14 and 33 (25%) were alive but did not answer the questionnaires. At day 90, 64% (87 out of 135) had completed the KCCQ, with no difference between the 2 groups (*P*=0.55); 18 (13%) died (9 in each group) before day 90, and 30 (26%) were alive but did not return the KCCQ. A complete case analysis showed no difference between the groups in general median patient satisfaction or the KCCQ overall summary score at day 14 or 90 (Table 2; Figure 4). Exploratory analysis of the clinical summary score and total symptom score revealed no statistically significant or clinically relevant between-group difference (Figure 4; Table S8)

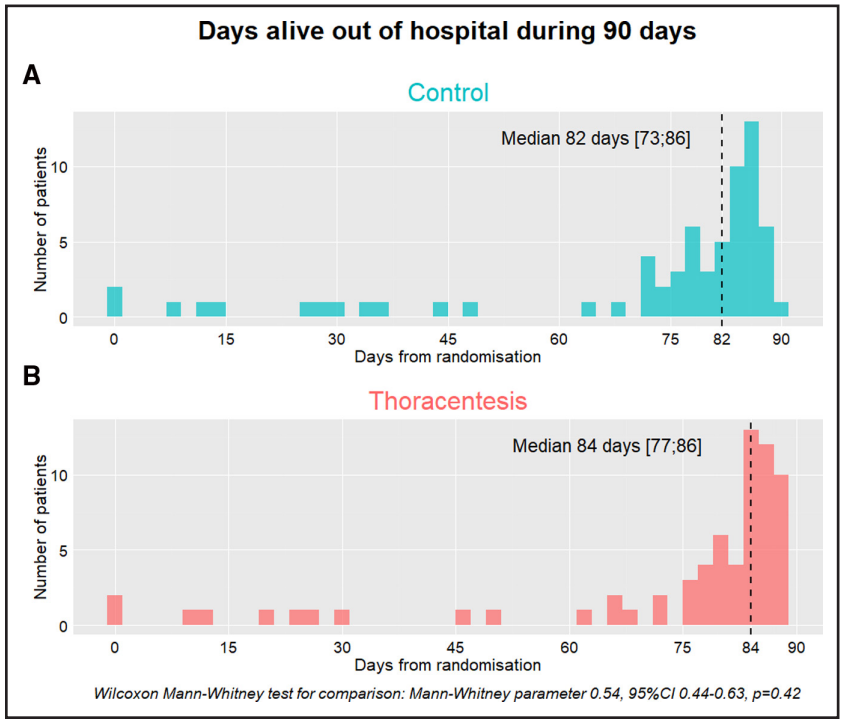

Figure 2. Distribution of days alive out of the hospital through 90 days according to randomization group. The histogram shows the distribution of the primary outcome of days alive out of the hospital through 90 days according to allocated treatment group. **A**, Control group. **B**, Thoracentesis group. The vertical dashed lines indicate the median values reported with the 25th and 75th percentile. Comparison by the Wilcoxon-Mann-Whitney test is given as the Mann-Whitney parameter with 95% CI. A 95% CI including 0.5 indicates no difference.

Table 2. Key Secondary Outcomes

Outcomes	Control group (n=67)	Thoracentesis group (n=68)	Estimate (95% CI)*	$P_{difference}$
Duration of index admission, d	5 (3; 8)	5 (3; 7)	0.48 (0.39–0.58)	0.69
Alive and not hospitalized because of heart failure within 90 d	84 (80; 86)	85 (81; 87)	0.57 (0.47–0.66)	0.16
90-d all-cause mortality	9 (13%)	9 (13%)	–	>0.99
Quality of life assessed by Kansas City Cardiomyopathy Questionnaire†				
Overall summary score, day 14	66 (41; 79)	57 (48; 73)	0.47 (0.35–0.60)	0.69
Overall summary score, day 90	79 (38; 91)	73 (54; 86)	0.50 (0.37–0.63)	0.98
Patient satisfaction questionnaire: "Are you satisfied with the overall hospitalization from admission to discharge?"†				
Score on a 5-point scale, day 14	4 (4; 5)	4 (4; 5)	0.47 (0.36–0.58)	0.59

Values are n (%), median (25th; 75th percentile), or Mann-Whitney parameter (95% CI).
*A 95% CI including 0.5 indicates no difference.
†Complete-case analysis.

Diuretic Therapy, Weight Loss, Renal Function, and GDMT Status by Discharge

One-third of the participants received oral loop diuretic treatment before admission (45 out of 135) with a median furosemide-equivalent dose of 80 mg (40; 120). Decongestion treatment during index admission was evaluated as the change in furosemide-equivalent dose of loop diuretic from preadmission to discharge dose. Furosemide-equivalent loop diuretic therapy was intensified by a median of 80 mg per day (40; 80) in both groups (P=0.85). There were no differences between groups in change from baseline to maximum daily dose of furosemide-equivalent loop diuretics administered during the index admission (160 mg [120; 240] in both groups; P=0.24). In both groups, the median furosemide equivalent dose of loop diuretics at discharge was 80 mg (interquartile range, 40–120; P=0.92). On admission, 37% in the control group and 29% in the thoracentesis group were on loop diuretics. At discharge, this proportion increased to 94% (63 out of 67) in the control group and 96% (65 out of 68) in the thoracentesis group. During the index admission, participants experienced a mean weight change of −4.5 kg (±4.0) in the control group and −5.0 kg (±3.6) in the thoracentesis group, with no difference between the 2 groups (P=0.41). Renal function at discharge did not differ between the groups. The median creatinine

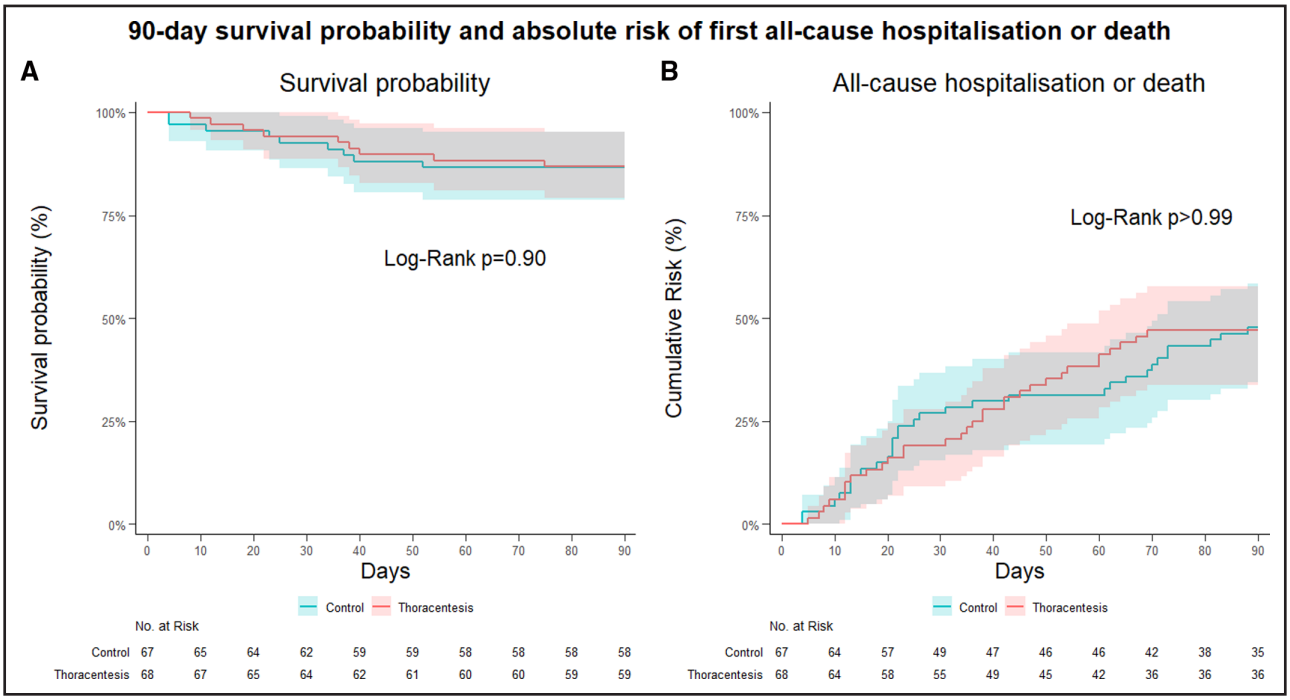

Figure 3. Ninety-day survival probability and absolute risk of first all-cause hospitalization or all-cause death.
Survival probability (**A**) and absolute risk of first all-cause hospitalization or all-cause death (**B**) during the 90 days after randomization according to the allocated treatment group. Comparisons are by log-rank test.

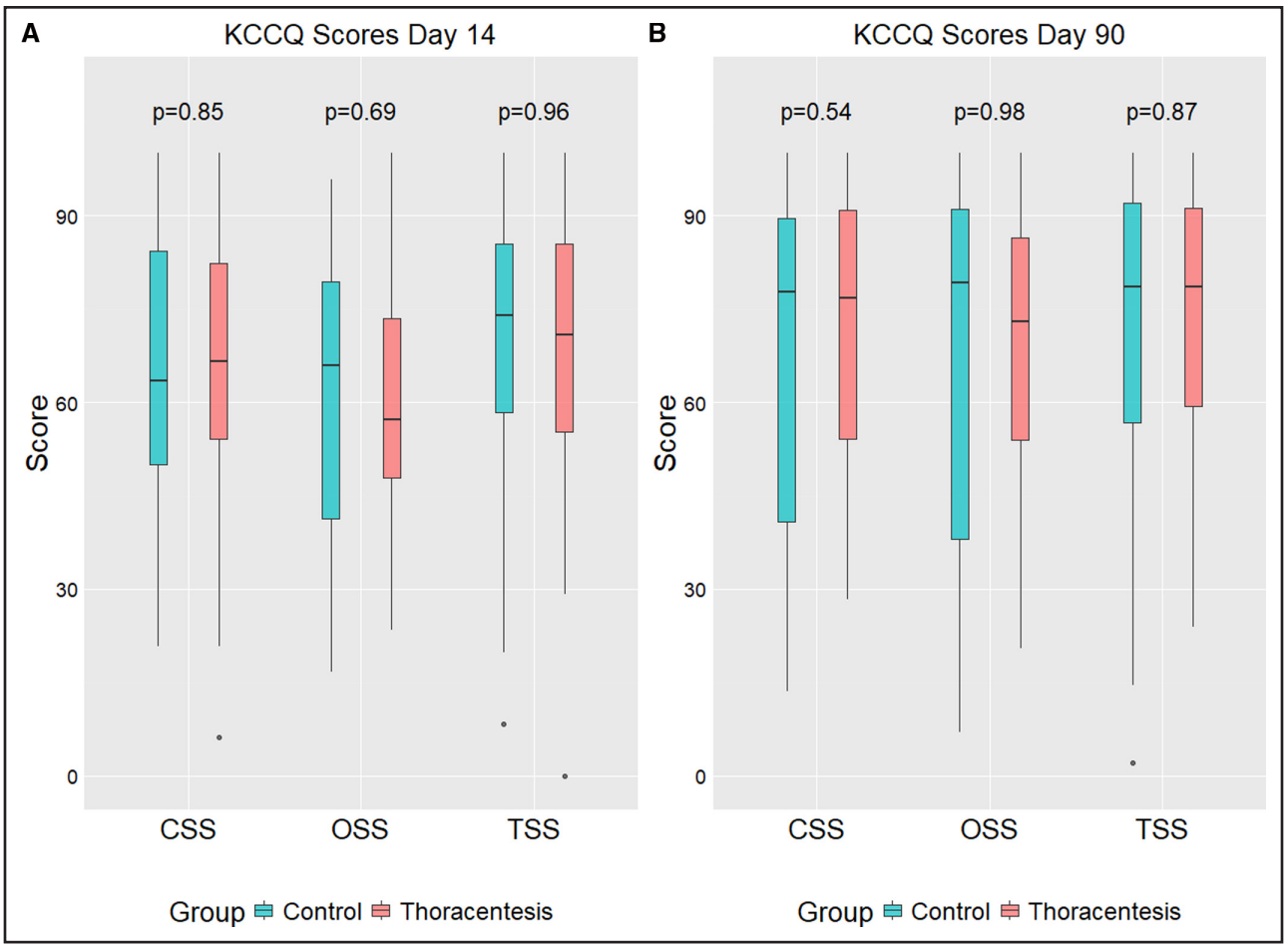

Figure 4. Patient-reported quality of life assessed by the Kansas City Cardiomyopathy Questionnaire 14 days after discharge and 90 days after randomization.

Comparison of clinical summary score (CSS), overall summary score (OSS), and total symptom score (TSS) according to allocated treatment group 14 days after discharge (**A**) and 90 days after randomization (**B**). The dark horizontal lines within the boxes indicate the median values. The upper and lower edges of the boxes correspond to the 75th and 25th percentiles, respectively. The whiskers extend from the edges to the largest and smallest value within ±1.5 times the interquartile range, and any data points beyond this range are represented as dots, indicating outliers. *P* values are from the Wilcoxon–Mann-Whitney test. KCCQ indicates Kansas City Cardiomyopathy Questionnaire.

level at discharge was 111 µmol/L (83; 140) in the control group compared with 106 (84; 128) µmol/L in the thoracentesis group (Mann-Whitney parameter, 0.45 [95% CI, 0.36–0.55]). There was no between-group difference in the status of GDMT at discharge (Table S9). The proportion of patients on angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor–neprilysin inhibitors increased from 53% to 71%, beta-blockers from 42% to 64%, mineralocorticoid receptor antagonists from 19% to 43%, and sodium-glucose cotransporter 2 inhibitors from 16% to 38%.

Safety Outcomes and Complications Attributable to Thoracentesis

Ten participants (7%) experienced a severe complication during the index admission (fall, pharmacologically treated delirium, nosocomial infection, or dehydration/electrolyte imbalance), with comparable rates between groups (details are available in Table S10).

During the trial period, 80 thoracenteses were performed in the study population. Control imaging was not protocolized but based on normal clinical practice and the individual physician's evaluation of the participant. An overview of the total complication rates and stratified by treatment group is presented in Table 3. Pneumothorax occurred in 4 out of 80 procedures (5%). Three were treated conservatively. One pneumothorax required intervention with a surgical drain and was classified as a serious adverse event. No major bleeding (hemothorax), organ laceration, intrapleural infection, or reexpansion pulmonary edema was observed, resulting in an overall rate of major complications of 1 out of 80 procedures (1%). However, in 20 out of the 80 thoracenteses (25%), participants experienced minor complications or discomfort during or after the procedure, resulting in an overall complication rate of 26% (21 out of 80).

Table 3. Complications of Thoracenteses Performed During the 90-Day Study Period

Complications	Total group (n=135)	Control group (n=67)	Thoracentesis group (n=68)
Thoracenteses performed during the study period†	80	15	65
Interventional thoracentesis or first procedure performed during index admission	64 (80)	5* (33)	59 (91)
Total complications of thoracentesis	21 (26)	3 (20)	18 (28)
Major	1 (1)	1 (7)	0 (0)
Minor	20 (25)	2	18
None	59 (74)	12	47
Complication type			
Pneumothorax	4 (5)	1 (7)	3 (5)
Conservative treatment	3 (4)	0	3
Need for a surgical drain	1 (1)	1	0
Pain or discomfort	10 (13)	1 (7)	9 (14)
Need for opioid analgesics	7 (9)	1	6
None or nonopioid analgesics	3 (4)	0	3
Catheter leakage	1 (1)	0 (0)	1 (2)
Accidental self-extubation	2 (3)	0 (0)	2 (3)
Minor puncture site bleeding	1 (1)	0 (0)	1 (2)
Intraprocedural: multiple needle punctures	3 (4)	1 (7)	2 (3)

Values are number (%) of procedures, with the total number of procedures during the study period as the denominator.
*The first procedure performed in 5 participants in the control group during the index admission.
†% is calculated with the total number of procedures during the study period as the denominator.

DISCUSSION

In this RCT of therapeutic thoracentesis in patients admitted to the hospital with acute heart failure with reduced LVEF and pleural effusion, a strategy of upfront thoracentesis did not increase DAOH in the following 90 days, or reduce the length of the index admission, the survival probability, or quality of life. Participants experienced minor complications or discomfort during or after the procedure in 25% of the total thoracenteses performed in the study period. Thoracentesis was safe, with a rate of serious complications of 1%, consistent with previous reports.[7–9]

No other randomized or controlled trials have assessed the effect of thoracentesis in patients hospitalized with heart failure with reduced LVEF and pleural effusion.

Our overall outcomes for the combined cohort align with results from observational and randomized trials of patients with acute decompensated heart failure. Previous smaller observational studies in patients with chronic heart failure undergoing thoracentesis (32 and 86 patients) have reported high 30-day mortality rates, ranging from 9% to 22%.[24,25] The observed 13% 90-day all-cause mortality rate in TAP-IT was similar to the 12% to 15% reported in a recent RCT evaluating the addition of acetazolamide to loop diuretic therapy in acute heart failure.[26] The observed KCCQ overall summary score 14 days after discharge was comparable with previous reports in patients with heart failure with reduced ejection fraction 1 week after hospitalization for worsening heart failure.[27] One observational study has reported improved quality of life associated with a reduction in pleural effusion measured by ultrasound in a small series of outpatients with heart failure receiving medical therapy.[28] Our observed mean KCCQ overall summary score on day 14 is ≈20 points higher than that reported during admission for acute heart failure[29]; however, the trajectory of health status measured by KCCQ shows a quick rebound after heart failure hospitalization in patients with heart failure with reduced ejection fraction.[30]

There are several possible explanations for the neutral outcome of TAP-IT. The population was elderly, with substantial comorbidities and frailty, which may partly explain the lack of effect of thoracentesis on DAOH. In fact, the 90-day all-cause hospitalization rate was 41%, with heart failure–related hospitalizations accounting for only 14% of the total rehospitalizations. Other trials on decongestive strategies and treatment have shown an effect on short-term outcome measures, such as congestion scores and responses to diuretics, but no effect on rehospitalization, mortality, or length of hospital stay.[26,31] The potential benefits of thoracentesis could have been reduced if the effusions were too small. Observational studies on the impact of thoracentesis by effusion size in patients with heart failure are small and have shown conflicting results. One study (n=10) indicated that symptom relief was more common in patients with effusions >1000 mL,[32] whereas others have found symptom relief and improvement in oxygenation regardless of the volume drained.[33,34] In TAP-IT, a pragmatic trial, the population reflects patients considered appropriate for thoracentesis on the basis of current clinical practice. The

result of TAP-IT reveals that the current population considered for thoracentesis does not seem to benefit from routine referral to thoracentesis and that the efficacy of the procedure in pleural effusion related to heart failure warrants investigation in more selective populations, perhaps on the basis of persisting symptoms, larger effusion volumes, or low tolerance of diuretics or GDMT.

Pleural effusion related to heart failure is associated with increased filling pressures, with a dose–response relationship between increased pulmonary capillary wedge pressure and central venous pressure and the size of pleural effusion.[5,35] Hence, reducing filling pressures should be the primary treatment target. A likely explanation for the lack of benefit from thoracentesis is that the intervention does not target the increased filling pressures responsible for the pleural effusion. Indeed, in TAP-IT, both groups received similar decongestive therapy and GDMT and demonstrated similar clinical outcomes. This underscores the importance of attention to goal-directed decongestion and fast implementation of GDMT to improve prognosis in patients hospitalized with heart failure.[36,37]

Limitations

The study has limitations. Unblinded interventional trials carry a risk of bias, and the primary outcome measure should be chosen carefully.[38] The primary outcome in TAP-IT, DAOH for 90 days, is clinically relevant and reasonably unbiased. Still, we cannot rule out that the unblinded nature of the trial could have affected the physician's incentive to discharge or to readmit. Furthermore, there is a risk of bias in patient-reported outcomes with overestimation of the effect of the intervention. Patient-reported quality of life is subject to survivor bias and attrition bias resulting from survey nonresponse, which primarily occurs in participants with compromised health status. In a frail study population with a high cardiovascular and noncardiovascular disease burden, this is a potential risk. We observed a greater variation in the primary outcome than anticipated, which reduced our statistical power to detect smaller or moderate differences between the groups, likely decreasing the statistical power from the expected 90%.

We do not have data on the completeness of decongestion or drainage; no protocolized decongestion assessment was used, and control imaging to assess the effect of decongestive treatment or thoracentesis is not performed routinely unless complications to thoracentesis are suspected. The median volume drained in TAP-IT was comparable to previous observational data, in which thoracentesis was associated with long-lasting symptom relief in stable outpatients with diuretic-resistant chronic heart failure and moderate to severe pleural effusion.[39] Thoracentesis was performed within a median of 22 hours, which was as expected, because half of the participants received anticoagulant therapy requiring a pause for up to 2 days before the procedure; in exploratory subgroup analysis, we found no numeric trend toward reduction in the length of the index admission in participants not on anticoagulant therapy. In a pragmatic trial, the results reflect not only the procedure but also the logistics around it at the participating sites. However, the volume drained by thoracentesis and the time to procedure reasonably represent what is experienced in the clinical setting. In addition, the results from this sample population may not be extrapolated to a younger population with heart failure as single morbidity, and the limited sample size does not allow conclusions based on subgroup analysis, including sex differences.

Conclusions

TAP-IT is the first RCT to investigate the effectiveness of thoracentesis in pleural effusion related to heart failure. In patients admitted to the hospital with heart failure with reduced ejection fraction and pleural effusion, a strategy of referral to routine thoracentesis did not increase the number of days the participants were alive and out of the hospital in the following 90 days. Thoracentesis was safe, with a rate of major complications of 1%, consistent with previous reports. Greater than expected variation in the primary outcome may limit the statistical power to detect smaller effect sizes. However, the current findings lay the groundwork for future research to confirm the results and further clarify the potential role of thoracentesis for patients with acute heart failure and pleural effusion.

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Supplemental Material

Methods
Tables S1–10
Figure S1
CONSORT checklist

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