

# Journal Club

## *Dapagliflozin for HFrEF*

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# Case

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- 75 year old man being discharged after hospitalization for acute decompensated HFrEF (LVEF 30%, s/p ICD)
- Multiple admissions in the past two years for HF
- History of CAD s/p DES x 2 to LAD 2 years ago, type 2 DM (Hgb A1c 8.0%), CKD stage 3, HTN, HLD, and a 30 pack year smoking history
- He is already on metoprolol, aspirin, atorvastatin, lisinopril, spironolactone, metformin, insulin, and daily furosemide
- Is there anything else can we add to reduce his risk of HF exacerbation?

# Search strategy

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Used Pubmed search with “heart failure with reduced ejection fraction”

7216 results

Filters - published past 6 months

721 results

Filter - core clinical journals

93 articles

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*Dapagliflozin in Patients with Heart Failure  
and Reduced Ejection Fraction*

McMurray JJV, Solomon SD, Inzucchi SE, et al.  
The New England Journal of Medicine

# Study characteristics

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- Large, randomized, placebo controlled trial of therapy
- Multicenter (410), multinational (20 countries)
- Analysis done by executive committee/Astra Zeneca
- Also by independent group at the University of Glasgow
- First large study of dapagliflozin with HFrEF at baseline +/- diabetes

# PICO

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- **Population:** Adults >18 years old; EF < 40%; NYHA class II, III, IV; on standard heart failure therapy; with and without diabetes
- **Intervention:** Dapagliflozin 10 mg
- **Comparison:** Placebo
- **Outcome:**
  - Primary: Cardiovascular death and hospitalization or urgent care visit
  - Secondary: Cardiovascular death and hospitalization

# Relevance and Context

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- Sodium-glucose cotransporter 2 (SGLT2) inhibitors
- ↓ hospitalizations for HF in type 2 DM
- Uncertain mechanism - possibly diuresis
- Little data on SGLT2 inhibitors in HFrEF patients in general
- Could potentially provide an additional treatment option for HFrEF

# Patients

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## **Inclusion criteria**

- Adults >18 years old +/- diabetes
- HFEF < 40%
- NYHA class II, III, IV
- On standard HF therapy:
- ICD +/- resynchronization
- ACEi/ARB/sacubitril-valsartan + BB (+ mineralocorticoid receptor antagonist)

## **Exclusion criteria**

- Recent treatment or side effects with SGLT2
- Symptomatic hypotension, SBP < 95, eGFR < 30, type 1 DM

**Table 1. Characteristics of the Patients at Baseline.\***

| Characteristic                           | Dapagliflozin<br>(N=2373) | Placebo<br>(N=2371) |
|--|---------------------------|---------------------|
| Age — yr                                 | 66.2±11.0                 | 66.5±10.8           |
| Female sex — no. (%)                     | 564 (23.8)                | 545 (23.0)          |
| Body-mass index†                         | 28.2±6.0                  | 28.1±5.9            |
| Race — no. (%)‡                          |                           |                     |
| White                                    | 1662 (70.0)               | 1671 (70.5)         |
| Black                                    | 122 (5.1)                 | 104 (4.4)           |
| Asian                                    | 552 (23.3)                | 564 (23.8)          |
| Other                                    | 37 (1.6)                  | 32 (1.3)            |
| Region — no. (%)                         |                           |                     |
| North America                            | 335 (14.1)                | 342 (14.4)          |
| South America                            | 401 (16.9)                | 416 (17.5)          |
| Europe                                   | 1094 (46.1)               | 1060 (44.7)         |
| Asia-Pacific                             | 543 (22.9)                | 553 (23.3)          |
| NYHA functional classification — no. (%) |                           |                     |
| II                                       | 1606 (67.7)               | 1597 (67.4)         |
| III                                      | 747 (31.5)                | 751 (31.7)          |
| IV                                       | 20 (0.8)                  | 23 (1.0)            |
| Heart rate — beats/min                   | 71.5±11.6                 | 71.5±11.8           |
| Systolic blood pressure — mm Hg          | 122.0±16.3                | 121.6±16.3          |
| Left ventricular ejection fraction — %   | 31.2±6.7                  | 30.9±6.9            |
| Median NT-proBNP (IQR) — pg/ml           | 1428 (857–2655)           | 1446 (857–2641)     |

## Principal cause of heart failure — no. (%)

|             |             |             |
|-------------|-------------|-------------|
| Ischemic    | 1316 (55.5) | 1358 (57.3) |
| Nonischemic | 857 (36.1)  | 830 (35.0)  |
| Unknown     | 200 (8.4)   | 183 (7.7)   |

## Medical history — no. (%)

|                                   |             |             |
|-----------------------------------|-------------|-------------|
| Hospitalization for heart failure | 1124 (47.4) | 1127 (47.5) |
| Atrial fibrillation               | 916 (38.6)  | 902 (38.0)  |
| Diabetes mellitus§                | 993 (41.8)  | 990 (41.8)  |

## Estimated GFR

|  |                 |                 |
|--|-----------------|-----------------|
| Mean — ml/min/1.73 m <sup>2</sup>                          | 66.0±19.6       | 65.5±19.3       |
| Rate of <60 ml/min/1.73 m <sup>2</sup> — no./total no. (%) | 962/2372 (40.6) | 964/2371 (40.7) |

## Device therapy — no. (%)

|   |            |            |
|---|------------|------------|
| Implantable cardioverter-defibrillator¶ | 622 (26.2) | 620 (26.1) |
| Cardiac resynchronization therapy       | 190 (8.0)  | 164 (6.9)  |

Image Citation: McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med.* 2019; [epub ahead of print]. Available from: <https://www.nejm.org/doi/full/10.1056/NEJMoa1911303>

**Table 1. (Continued.)**

| <b>Characteristic</b>                                    | <b>Dapagliflozin<br/>(N = 2373)</b> | <b>Placebo<br/>(N = 2371)</b> |
|--|-------------------------------------|-------------------------------|
| <b>Heart failure medication — no. (%)</b>                |                                     |                               |
| Diuretic   | 2216 (93.4)                         | 2217 (93.5)                   |
| ACE inhibitor  | 1332 (56.1)                         | 1329 (56.1)                   |
| ARB  | 675 (28.4)                          | 632 (26.7)                    |
| Sacubitril–valsartan                                     | 250 (10.5)                          | 258 (10.9)                    |
| Beta-blocker   | 2278 (96.0)                         | 2280 (96.2)                   |
| Mineralocorticoid receptor antagonist                    | 1696 (71.5)                         | 1674 (70.6)                   |
| Digitalis  | 445 (18.8)                          | 442 (18.6)                    |
| <b>Glucose-lowering medication — no./total no. (%)**</b> |                                     |                               |
| Biguanide  | 504/993 (50.8)                      | 512/990 (51.7)                |
| Sulfonylurea   | 228/993 (23.0)                      | 210/990 (21.2)                |
| DPP-4 inhibitor  | 161/993 (16.2)                      | 149/990 (15.1)                |
| GLP-1 receptor agonist                                   | 11/993 (1.1)                        | 10/990 (1.0)                  |
| Insulin  | 274/993 (27.6)                      | 266/990 (26.9)                |

Image Citation: McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019; [epub ahead of print]. Available from: <https://www.nejm.org/doi/full/10.1056/NEJMoa1911303>

# Intervention and Comparison

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- Randomized to dapagliflozin 10 mg or placebo
- Evaluated at 14 days, 60 days, 4 months, and 4 month intervals after
- Discontinued if DKA or pregnancy
- Dose temporarily reduced to 5 mg or held if needed clinically

Hypotension, volume depletion, AKI

# Outcomes

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## Primary

- **Hospitalization/urgent care visit + CV death**

## Secondary

- **Hospitalization + CV death**
- Total # hospitalizations
- CV deaths
- Kansas City Cardiomyopathy Questionnaire scores at 0 and 8 months
- ↓ renal fx + death from any cause

# Study Validity

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- + Patients randomized
- + Randomization concealed to patients
- + Intention-to-treat was followed
- + Similar characteristics of both groups
- + Similar prognosis of both groups
- + Good follow up (89% and 88%)
- Study personnel were aware of allocation
- Study was funded by Astra Zeneca which could cause bias
- Very few class NYHA IV enrolled in study
- Reduced dosing protocol might have masked potential adverse events

# Results

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## Primary:

- 386 (16.3%) dapagliflozin vs. 502 (21.2%) placebo  $p < 0.001$  NNT - 21

## Secondary:

- 382 (16.1%) dapagliflozin vs. 495 (20.9%) placebo:  $p < 0.001$ , NNT - 21
- All individual event rates were less in dapagliflozin group
- KCCQ scores were significantly better in dapagliflozin group
- Adverse events were not significantly different

**Table 2. Primary and Secondary Cardiovascular Outcomes and Adverse Events of Special Interest.\***

| Variable   | Dapagliflozin<br>(N = 2373) |                          | Placebo<br>(N = 2371) |                          | Hazard or Rate Ratio<br>or Difference<br>(95% CI) | P Value |
|--|-----------------------------|--------------------------|-----------------------|--------------------------|---|---------|
|  | no. (%)                     | events/100<br>patient-yr | no. (%)               | events/100<br>patient-yr |   |         |
| <b>Efficacy outcomes</b>   |                             |                          |                       |                          |   |         |
| Primary composite outcome — no. (%)†                                       | 386 (16.3)                  | 11.6                     | 502 (21.2)            | 15.6                     | 0.74 (0.65 to 0.85)                               | <0.001  |
| Hospitalization or an urgent visit for heart failure                       | 237 (10.0)                  | 7.1                      | 326 (13.7)            | 10.1                     | 0.70 (0.59 to 0.83)                               | NA      |
| Hospitalization for heart failure  | 231 (9.7)                   | 6.9                      | 318 (13.4)            | 9.8                      | 0.70 (0.59 to 0.83)                               | NA      |
| Urgent heart-failure visit   | 10 (0.4)                    | 0.3                      | 23 (1.0)              | 0.7                      | 0.43 (0.20 to 0.90)                               | NA      |
| Cardiovascular death   | 227 (9.6)                   | 6.5                      | 273 (11.5)            | 7.9                      | 0.82 (0.69 to 0.98)                               | NA      |
| <b>Secondary outcomes</b>  |                             |                          |                       |                          |   |         |
| Cardiovascular death or heart-failure hospitalization — no. (%)            | 382 (16.1)                  | 11.4                     | 495 (20.9)            | 15.3                     | 0.75 (0.65 to 0.85)                               | <0.001  |
| Total no. of hospitalizations for heart failure and cardiovascular deaths‡ | 567                         | —                        | 742                   | —                        | 0.75 (0.65 to 0.88)                               | <0.001  |
| Change in KCCQ total symptom score at 8 mo§                                | 6.1±18.6                    | —                        | 3.3±19.2              | —                        | 1.18 (1.11 to 1.26)                               | <0.001  |
| Worsening renal function — no. (%)¶  | 28 (1.2)                    | 0.8                      | 39 (1.6)              | 1.2                      | 0.71 (0.44 to 1.16)                               | NA      |
| Death from any cause — no. (%)   | 276 (11.6)                  | 7.9                      | 329 (13.9)            | 9.5                      | 0.83 (0.71 to 0.97)                               | NA      |
| <b>Safety outcomes  </b>   |                             |                          |                       |                          |   |         |
| Discontinuation due to adverse event — no./total no. (%)                   | 111/2368 (4.7)              | —                        | 116/2368 (4.9)        | —                        | —   | 0.79    |
| <b>Adverse events of interest — no./total no. (%)</b>                      |                             |                          |                       |                          |   |         |
| Volume depletion   | 178/2368 (7.5)              | —                        | 162/2368 (6.8)        | —                        | —   | 0.40    |
| Renal adverse event  | 153/2368 (6.5)              | —                        | 170/2368 (7.2)        | —                        | —   | 0.36    |
| Fracture   | 49/2368 (2.1)               | —                        | 50/2368 (2.1)         | —                        | —   | 1.00    |
| Amputation   | 13/2368 (0.5)               | —                        | 12/2368 (0.5)         | —                        | —   | 1.00    |
| Major hypoglycemia**   | 4/2368 (0.2)                | —                        | 4/2368 (0.2)          | —                        | —   | NA      |
| Diabetic ketoacidosis††  | 3/2368 (0.1)                | —                        | 0                     | —                        | —   | NA      |
| Fournier's gangrene  | 0                           | —                        | 1/2368 (<0.1)         | —                        | —   | NA      |

Figure Citation: McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med.* 2019; [epub ahead of print]. Available from: <https://www.nejm.org/doi/full/10.1056/NEJMoa1911303>

# Are these results applicable to the patient?

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- Age of trial participants was around 66 +/- 11
- Most of his medications were included in the baseline characteristics
- He is NYHA class II or III, EF < 40%, and would not be excluded on his degree of CKD
- Would discuss risks and benefits of the medication
- He could benefit in terms of his diabetes and HFrEF
- Will need monitoring of renal function and for symptoms of hypotension

# Conclusion

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- Dapagliflozin is a good option in patients with diabetes and HFrEF
- May be a safe and effective medication to add to select patient regimens without diabetes
- Appears to reduce both hospitalizations and cardiovascular death
- Adverse events commonly associated with SGLT2 inhibitors were not significantly different from placebo

# References

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1. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019; [epub ahead of print]. Available from: <https://www.nejm.org/doi/full/10.1056/NEJMoa1911303>
2. Schwartz MD, Dowell D, Aperi J, et al. Improving journal club presentations, or, I can present that paper in under 10 minutes. BMJ Evidence-Based Medicine. 2007;12:66-68.

# Diagnostic Accuracy of Point-of-Care Lung Ultrasonography and Chest Radiography in Adults With Symptoms Suggestive of Acute Decompensated Heart Failure

Maw AM, Hassanin A, Ho PM, et al

October 2019 Journal Club

Presented by Michelle Sausner, DO

# Introduction

Objective: To compare the accuracy of lung ultrasound with the accuracy of CXR in the diagnosis of cardiogenic pulmonary edema in adult patients presenting with dyspnea

# Acute Decompensated Heart Failure

- Clinical syndrome of new or worsening signs and symptoms of HF
- One of leading reasons for ED visits in US

## Major Causes:

- ACS
- Myocarditis
- Acute valve syndromes
- Progressive valve disease
- Cardiomyopathies
- Poorly controlled hypertension

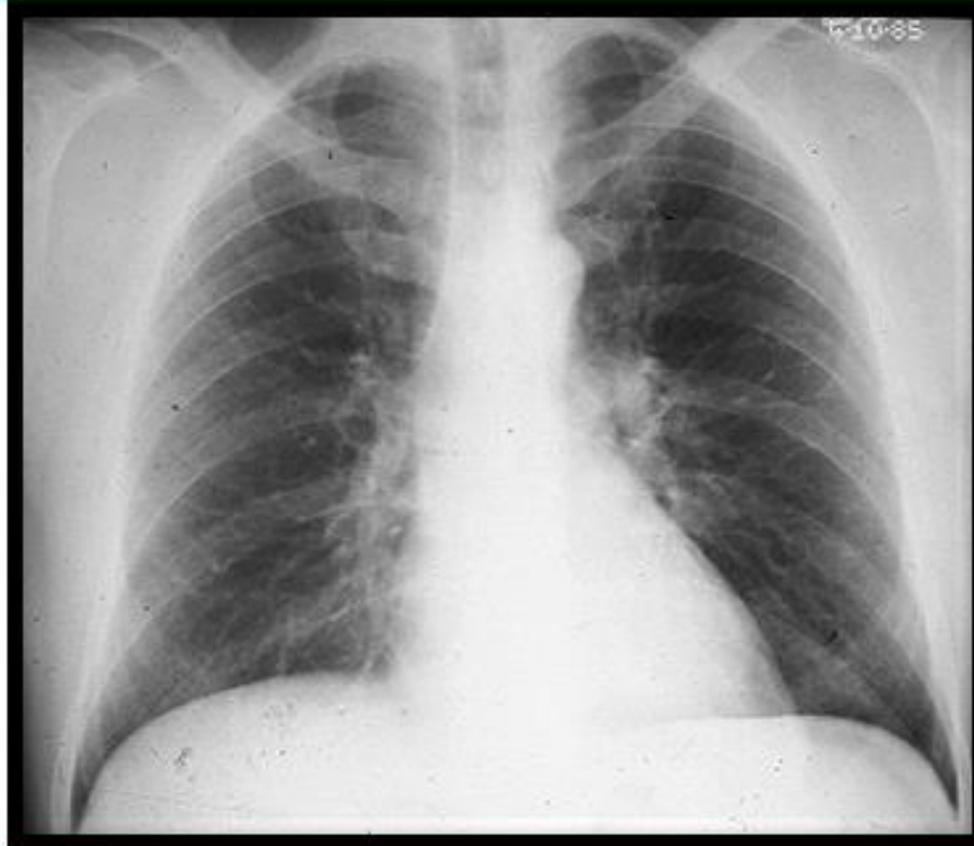
## Clinical Manifestations:

- Acute dyspnea, orthopnea, tachypnea, tachycardia, hypertension
- Accessory muscle usage
- Diffuse pulmonary crackles
- S3, elevated JVP, and/or peripheral edema
- Hypotension (severe disease)
- Assess for inadequate peripheral or end-organ perfusion

# Diagnosing ADHF

- EKG
- CXR
- Labs: CBC, troponins, electrolytes (Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>, HCO<sub>3</sub><sup>-</sup>), BUN, creatinine, ABG, LFTs, BNP/NT-proBNP
- Bedside echo if cardiac/valvular function not known

## Normal chest radiograph

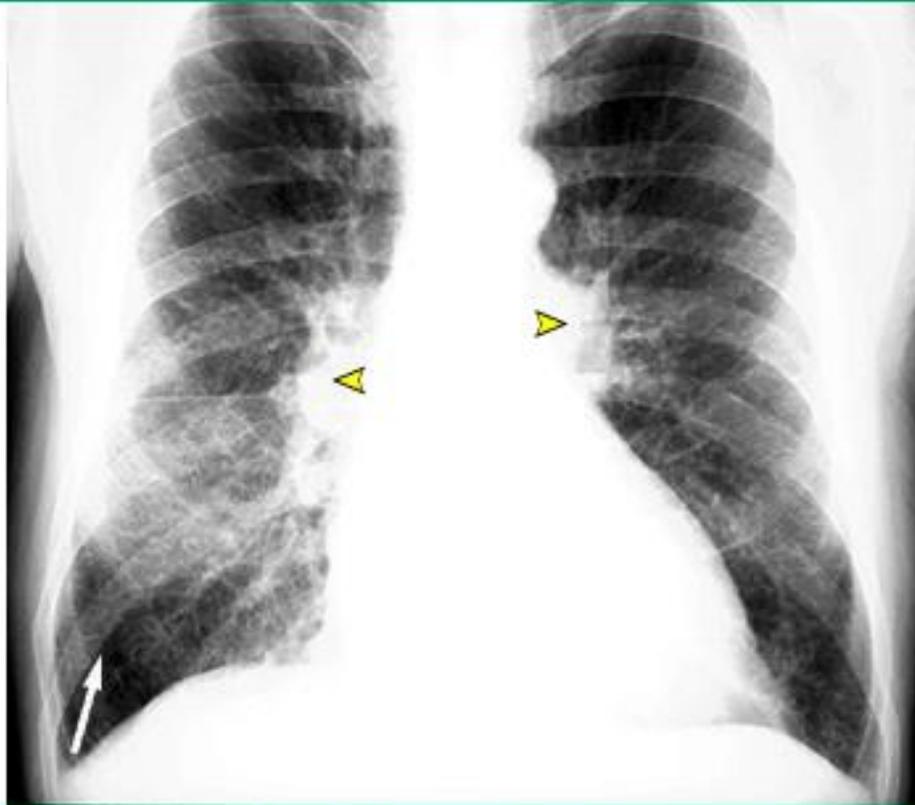


Posteroanterior view of a normal chest radiograph.

*Courtesy of Carol M Black, MD.*

## Heart failure

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This chest radiograph of a 65-year-old male with dyspnea and orthopnea demonstrates mild pulmonary vascular congestion, septal lymphatic distention (arrow), interstitial veiling, and enlarged hilar shadows (arrowhead), indicative of left ventricular decompensation.

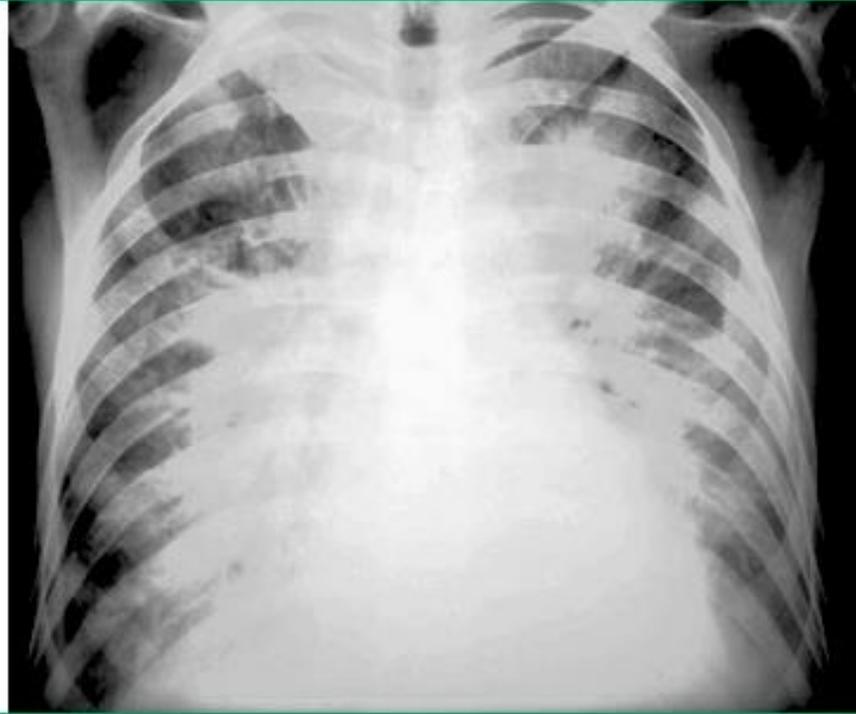
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*Courtesy of Jonathan Kruskal, MD.*

UpToDate®

## Acute left ventricular failure

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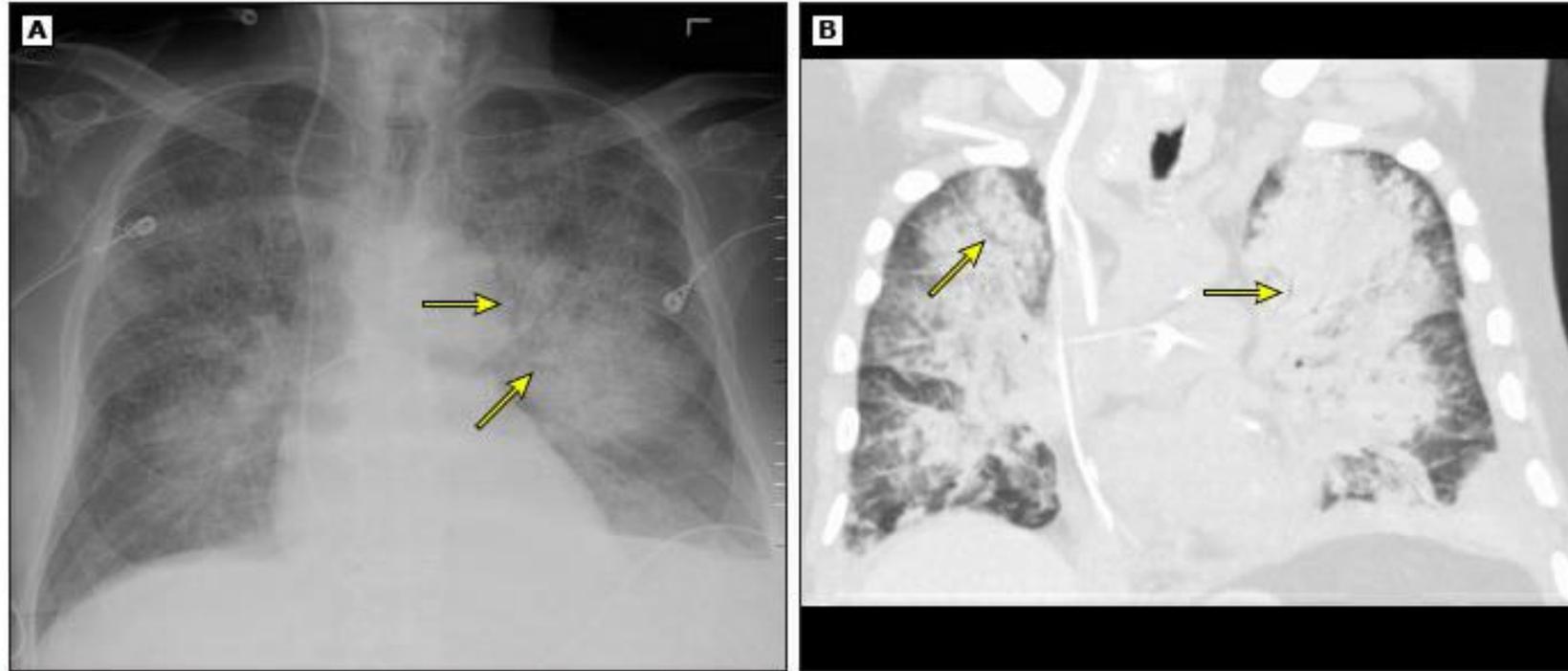


This plain frontal radiograph of the chest of a 30-year-old male demonstrates bilateral perihilar alveolar edema, giving a typical butterfly appearance, with bilateral interstitial edema and pulmonary venous redistribution to the upper lobes. The acute nature of this condition is manifest by the absence of pleural effusions or an enlarged cardiac silhouette.

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*Photo courtesy of Jonathan Kruskal, MD.*

## Radiograph and CT of acute pulmonary edema



(A) An anteroposterior radiograph shows perihilar consolidations and air bronchograms (arrows) of acute alveolar edema.

(B) A coronal reconstruction of a CT scan of the same patient shows acute alveolar edema with diffuse perihilar infiltrates and air bronchograms (arrows).

CT: computed tomography.

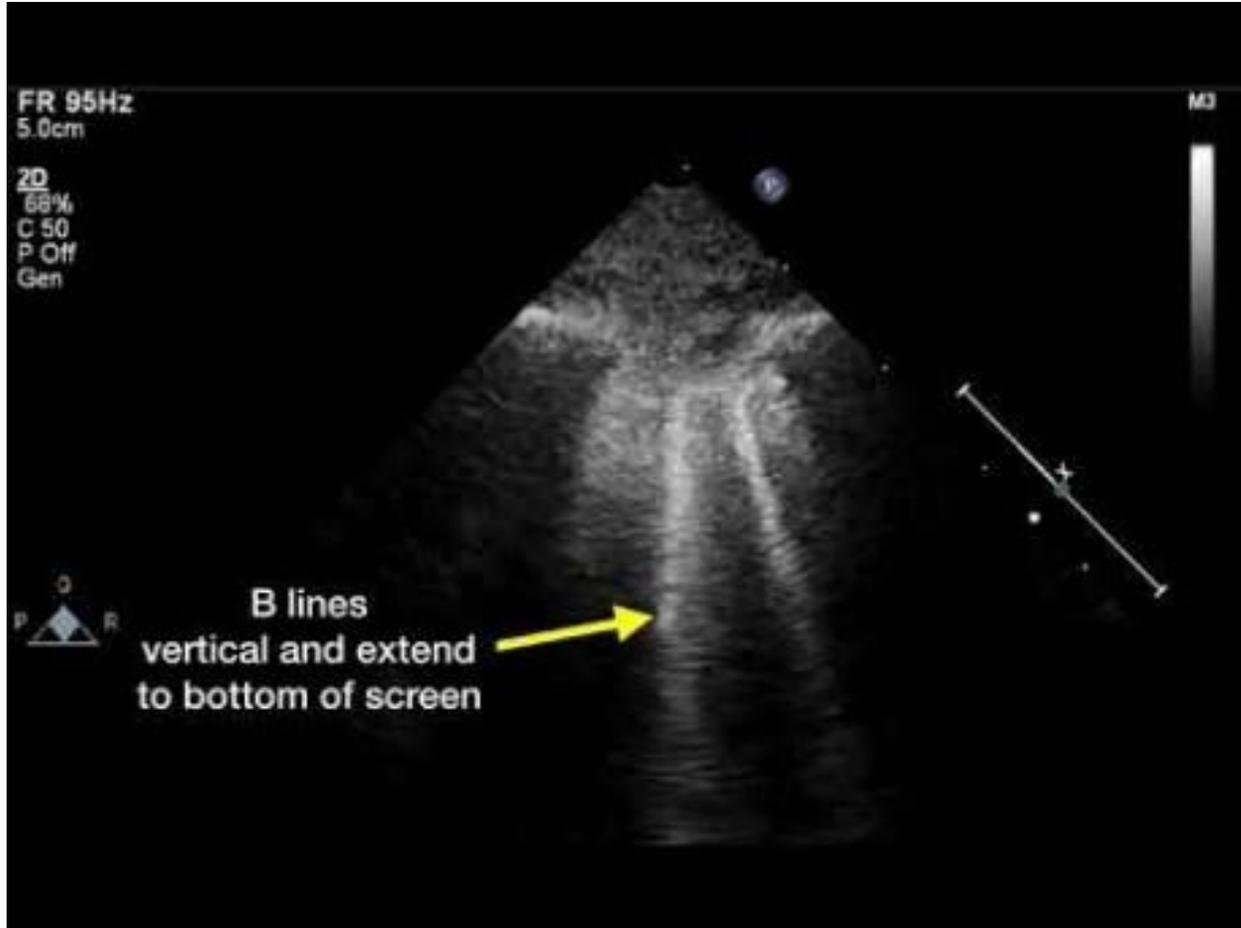


Figure 1. Ultrasound demonstrating A-line artifacts, a repetitive reverberation artifact of the pleura

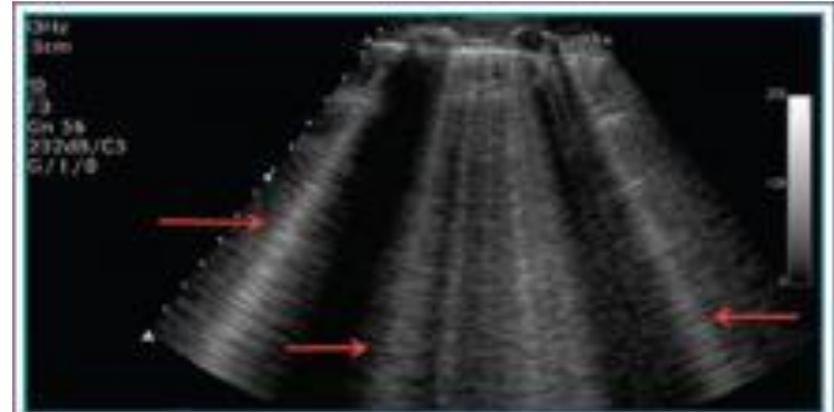


Figure 3. Ultrasound showing bilateral B lines, commonly seen in lungs with interstitial edema

# Study Selection

- Inclusion criteria: prospective adult cohort presenting to any clinical setting with dyspnea who underwent both LUS and CXR on initial assessment
- Two reviewers independently assessed the studies for inclusion criteria
- Each article assessed for:
  1. Patient selection
  2. CXR
  3. Lung ultrasound
  4. Medical record audit
- Two possible sources of variability between studies:
  1. Spectrum of disease
  2. Threshold effect

|                      | Disease                         | No Disease                      |
|----------------------|---------------------------------|---------------------------------|
| Positive Test Result | True Positive<br>( <i>TP</i> )  | False Positive<br>( <i>FP</i> ) |
| Negative Test Result | False Negative<br>( <i>FN</i> ) | True Negative<br>( <i>TN</i> )  |

**Sensitivity** =  $TP / (TP + FN)$

**Specificity** =  $TN / (TN + FP)$

**PPV** =  $TP / (TP + FP)$

**NPV** =  $TN / (FN + TN)$

# Main Outcomes, Measures, and Results

- Comparative accuracy of LUS and CXR in diagnosing ADHF as measured by the differences between the 2 modalities in pooled sensitivity and specificity
- Six studies met inclusion criteria, representing 1827 patients
  - Number of LUS operators ranged from 1 to at least 12
  - 4 studies – sonographers blinded to all clinical info except what was seen at the bedside and US images
  - 2 studies – LUS expert blinded to all clinical info interpreted previously recorded images

|             | <b>Lung<br/>Ultrasound</b> | <b>Chest<br/>Radiography</b> |
|-------------|----------------------------|------------------------------|
| Sensitivity | 0.88                       | 0.73                         |
| Specificity | 0.90                       | 0.90                         |

# Conclusions

- Lung ultrasound superior, positive likelihood ratio of 8.6 (7.4 for CXR) and negative likelihood ratio of 0.1 (0.3 for CXR)
- LUS is more sensitive than CXR (0.88 vs. 0.73) in detecting pulmonary edema in acute decompensated heart failure (ADHF). No difference in specificity.
- For every 100 patients presenting with pulmonary edema, LUS can diagnose 15 more cases than CXR without an increase in the number of false positives
- LUS should be considered as an adjunct imaging modality in the evaluation of patients with dyspnea at risk of ADHF

# Limitations

- Number of including studies
- Risk of bias in some domains
- Unclear/incomplete blinding of LUS/CXR
- Lung ultrasound wide sensitivity (0.58-0.97)
- Inconsistent results
  - Convenience sampling
  - Experience ultrasound operators

# Sources

- Maw AM, Hassanin A, Ho PM, et al. Diagnostic Accuracy of Point-of-Care Lung Ultrasonography and Chest Radiography in Adults With Symptoms Suggestive of Acute Decompensated Heart Failure: A Systematic Review and Meta-analysis. *JAMA Netw Open*. Published online March 15, 2019;2(3):e190703. doi:10.1001/jamanetworkopen.2019.0703
- Meyer, TE. Approach to acute decompensated heart failure in adults. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2019
- Taylor, T., Meer, J., Beck, S. Lung ultrasound takes 2 to 3 minutes to perform and can help narrow down the differential in a patient with dyspnea. *Emergency Medicine*. 2015 January;47(1):35-36