#AHA23

MAYO CLINIC

# Screening For Peripartum Cardiomyopathies Using An AI-Enhanced Digital Stethoscope: A Randomized Clinical Trial

NCT05438576

Demilade Adedinsewo, MD, MPH| Mayo Clinic, Florida

American Heart Association.

# DISCLOSURES


- Dr. Adedinsewo is supported by the Mayo Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Program funded by the National Institutes of Health [grant number K12 HD065987].
- This trial was funded by Mayo Clinic (Centers for Digital Health and Community Health and Engagement Research) and in part by the Mayo Clinic BIRCWH Program
- Portable ECG, phonocardiogram recordings, and AI predictions using the digital stethoscope were extracted by the Eko Health team and sent to the coordinating center for analysis. Eko Health had no role in study design, data collection, data analysis, or data interpretation.

# BACKGROUND

- Cardiovascular disease is a leading cause of death during pregnancy and postpartum
- In the U.S., cardiomyopathy is a key contributor
  - 2nd leading cause of death among Black women
  - Leading cause of death in the late postpartum period for all women
- Nigeria has the highest reported incidence of peripartum cardiomyopathy – 1 in 100 livebirths
- Diagnosis is challenging which leads to delayed recognition
- Symptoms due to physiologic adaptations of pregnancy often overlap with heart failure

*Petersen EE et al. Vital Signs: Pregnancy-Related Deaths, United States, 2011–2015, and Strategies for Prevention, 13 States, 2013–2017. MMWR Morb Mortal Wkly Rep 2019;
*Trost et al. Pregnancy-Related Deaths: Data from Maternal Mortality Review Committees in 36 US States, 2017–2019. CDC;
*Karaye et al. Clinical Features and Outcomes of Peripartum Cardiomyopathy in Nigeria. J Am Coll Cardiol. 2020

# BACKGROUND

- Global maternal mortality has remained either stagnant or worsened in many regions of the world
- Sub-Saharan Africa bears the highest burden of maternal deaths (70%)
  - South Sudan
  - Chad
  - Nigeria

  } Extremely high

    - highest absolute # of deaths @ 82,000 in 2020
- US maternal mortality rate is higher than other developed countries – trending up over the past 3 decades

Moyer et al. Stalled progress in reducing maternal mortality globally: what next?, Lancet Mar 2023
Trends in maternal mortality 2000 to 2020: estimates by WHO, UNICEF, UNFPA, World Bank Group and UNDESA/Population Division.

# U.S MATERNAL MORTALITY

**Events per 100,000 live births**

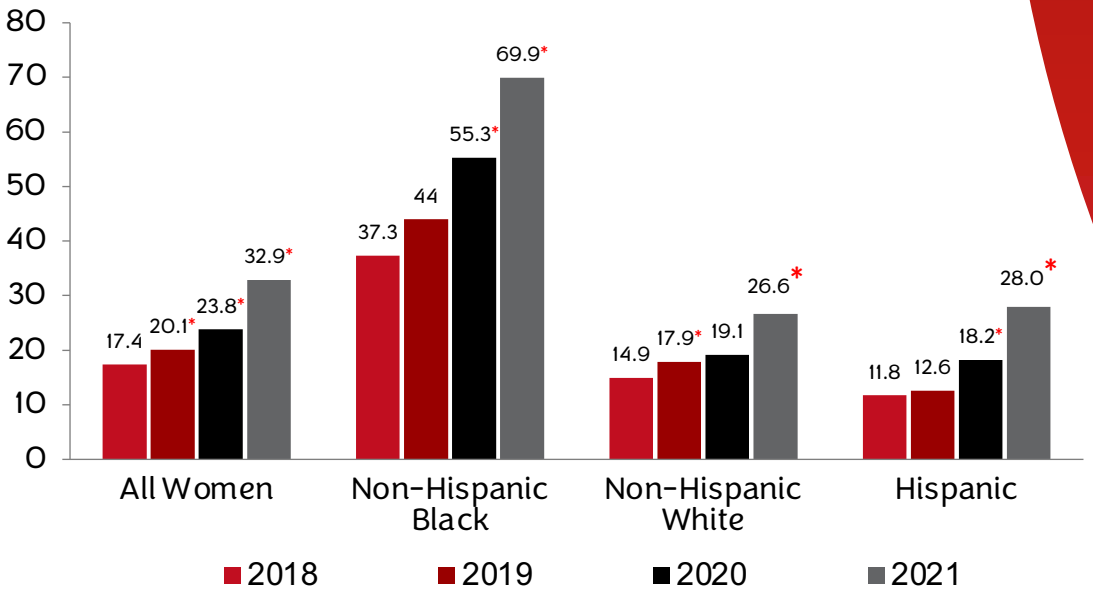
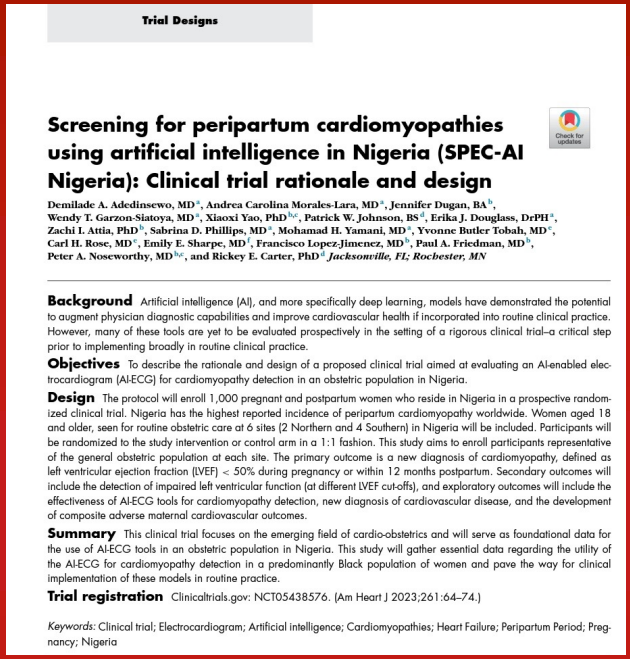



Figure re-created using data from the National Center for Health Statistics. Hoyert, Donna L. Maternal Mortality Rates in the United States, 2021. Published: 03/16/2023, URL : https://stacks.cdc.gov/view/cdc/124678

# METHODS

- We designed an open label, randomized, pragmatic clinical trial to evaluate the impact of AI guided screening on the diagnosis of pregnancy related left ventricular dysfunction (LVSD)
- Pregnant and postpartum women enrolled at six (6) sites were randomized in a 1:1 fashion to
  - Control arm
  - Intervention arm
- The primary endpoint was detection of LVSD, defined as left ventricular ejection fraction (LVEF) <50% by echocardiography.
- Trial Registration number: NCT05438576



Trial Designs

**Screening for peripartum cardiomyopathies using artificial intelligence in Nigeria (SPEC-AI Nigeria): Clinical trial rationale and design**

Demilade A. Adedinsewo, MD[a], Andrea Carolina Morales-Lara, MD[a], Jennifer Dugan, BA[b], Wendy T. Garzon-Siatoya, MD[a], Xiaoxi Yao, PhD[b,c], Patrick W. Johnson, BS[d], Erika J. Douglass, DrPH[a], Zachi I. Attia, PhD[b], Sabrina D. Phillips, MD[a], Mohamad H. Yamani, MD[a], Yvonne Butler Tobah, MD[e], Carl H. Rose, MD[e], Emily E. Sharpe, MD[f], Francisco Lopez-Jimenez, MD[b], Paul A. Friedman, MD[b], Peter A. Noseworthy, MD[b,c], and Rickey E. Carter, PhD[d] *Jacksonville, FL; Rochester, MN*

**Background** Artificial intelligence (AI), and more specifically deep learning, models have demonstrated the potential to augment physician diagnostic capabilities and improve cardiovascular health if incorporated into routine clinical practice. However, many of these tools are yet to be evaluated prospectively in the setting of a rigorous clinical trial–a critical step prior to implementing broadly in routine clinical practice.

**Objectives** To describe the rationale and design of a proposed clinical trial aimed at evaluating an AI-enabled electrocardiogram (AI-ECG) for cardiomyopathy detection in an obstetric population in Nigeria.

**Design** The protocol will enroll 1,000 pregnant and postpartum women who reside in Nigeria in a prospective randomized clinical trial. Nigeria has the highest reported incidence of peripartum cardiomyopathy worldwide. Women aged 18 and older, seen for routine obstetric care at 6 sites (2 Northern and 4 Southern) in Nigeria will be included. Participants will be randomized to the study intervention or control arm in a 1:1 fashion. This study aims to enroll participants representative of the general obstetric population at each site. The primary outcome is a new diagnosis of cardiomyopathy, defined as left ventricular ejection fraction (LVEF) < 50% during pregnancy or within 12 months postpartum. Secondary outcomes will include the detection of impaired left ventricular function (at different LVEF cut-offs), and exploratory outcomes will include the effectiveness of AI-ECG tools for cardiomyopathy detection, new diagnosis of cardiovascular disease, and the development of composite adverse maternal cardiovascular outcomes.

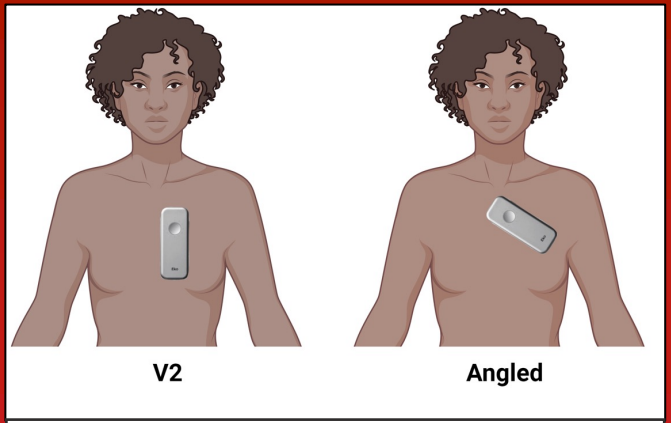
**Summary** This clinical trial focuses on the emerging field of cardio-obstetrics and will serve as foundational data for the use of AI-ECG tools in an obstetric population in Nigeria. This study will gather essential data regarding the utility of the AI-ECG for cardiomyopathy detection in a predominantly Black population of women and pave the way for clinical implementation of these models in routine practice.

**Trial registration** Clinicaltrials.gov: NCT05438576. (Am Heart J 2023;261:64–74.)

*Keywords:* Clinical trial; Electrocardiogram; Artificial intelligence; Cardiomyopathies; Heart Failure; Peripartum Period; Pregnancy; Nigeria

# METHODS

- **'Attention' Control arm:** Standard 12-lead ECG* + Usual care
- **Intervention:** Standard 12-lead ECG* + Artificial intelligence enabled digital stethoscope recordings (ECG + phonocardiogram) at the point of care with AI results for LVSD available in real-time
  - Digital stethoscope recordings taken at:
    - V2 position
    - Angled
    - Handheld
  - Baseline echocardiograms obtained as part of the study protocol to assess the diagnostic performance of the AI-ECG
- The control arm received standard 12-lead ECGs* (including AI-predictions for age and sex) to control for the potential benefit that receiving an ECG might introduce to the study



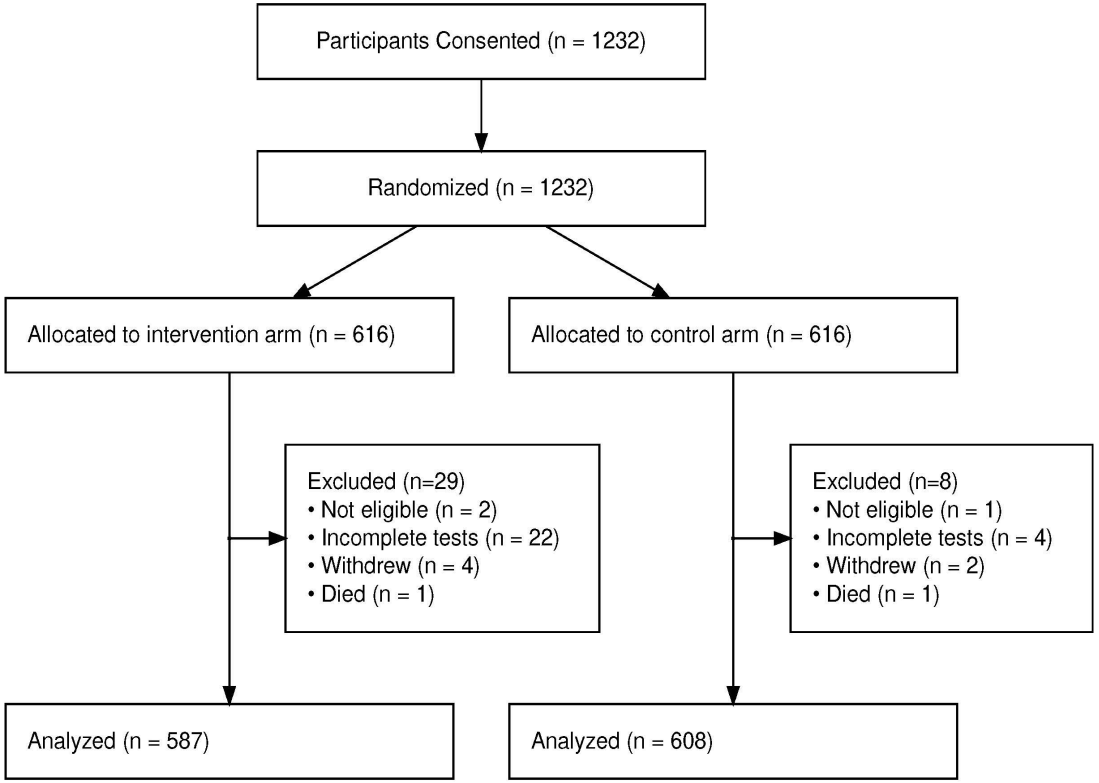


*Attia et al. Age and Sex Estimation Using Artificial Intelligence From Standard 12-Lead ECGs. Circ Arrhythm Electrophysiol. 2019 Sep;12(9)

# RESULTS

587 women were assigned to the intervention arm and 608 to the control arm.

The primary analysis was conducted using the modified intention to treat principle. To be included in the analysis, the participant needs to be randomized and complete at least the baseline assessments and testing.



# RESULTS

| Characteristic | N | Intervention Arm (N=587) | Control Arm (N=608) |
|---|---|---|---|
| Age (IQR), years | 1,195 | 31 (27-35) | 31 (26-35) |
| Race (Black) – no. (%) | 1,195 | 587 (100.0%) | 608 (100.0%) |
| Status at Study Entry – no. (%) | 1,195 | | |
| – Pregnant | | 423 (72.1%) | 451 (74.2%) |
| – Postpartum | | 164 (27.9%) | 157 (25.8%) |
| Weight (IQR), kg | 1,195 | 70 (60-80) | 70 (60-83) |
| Height (IQR), cm | 1,195 | 161 (157-165) | 161 (157-165) |
| SBP (IQR), mmHg | 1,193 | 110 (100-120) | 110 (100-120) |
| DBP (IQR), mmHg | 1,193 | 70 (60-80) | 70 (60-80) |
| Resting heart rate (IQR), bpm | 1,195 | 87 (80-95) | 88 (80-95) |
| Hemoglobin (IQR), g/dL | 1,016 | 11 (10-12) | 11 (10-12) |
| Hematocrit (IQR), % | 1,056 | 33 (30-35) | 33 (30-35) |
| Urinalysis + for protein – no. (%) | 1,147 | 61 (10.9%) | 62 (10.6%) |
| Chronic hypertension | 1,195 | 27 (4.6%) | 23 (3.8%) |
| Gestational hypertension | 1,195 | 24 (4.1%) | 28 (4.6%) |
| Preeclampsia | 1,194 | 19 (3.2%) | 18 (3.0%) |
| Eclampsia | 1,195 | 6 (1.0%) | 4 (0.7%) |
| Gestational diabetes | 1,195 | 5 (0.9%) | 12 (2.0%) |

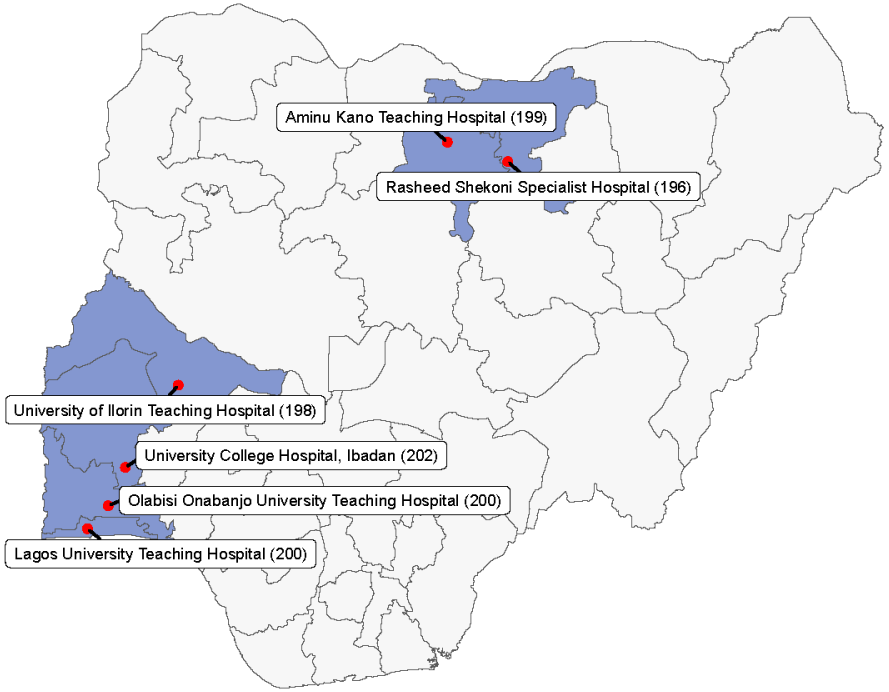
# RESULTS (Primary)

A total of 1,195 participants enrolled across six teaching hospital in Nigeria were included in the final analysis

The primary endpoint was detected in

- 24 (4.1%) patients in the intervention arm and
- 11 (1.8%) patients in the control arm.

AI-guided screening (digital stethoscope maximum prediction across all locations recorded) doubled cardiomyopathy detection

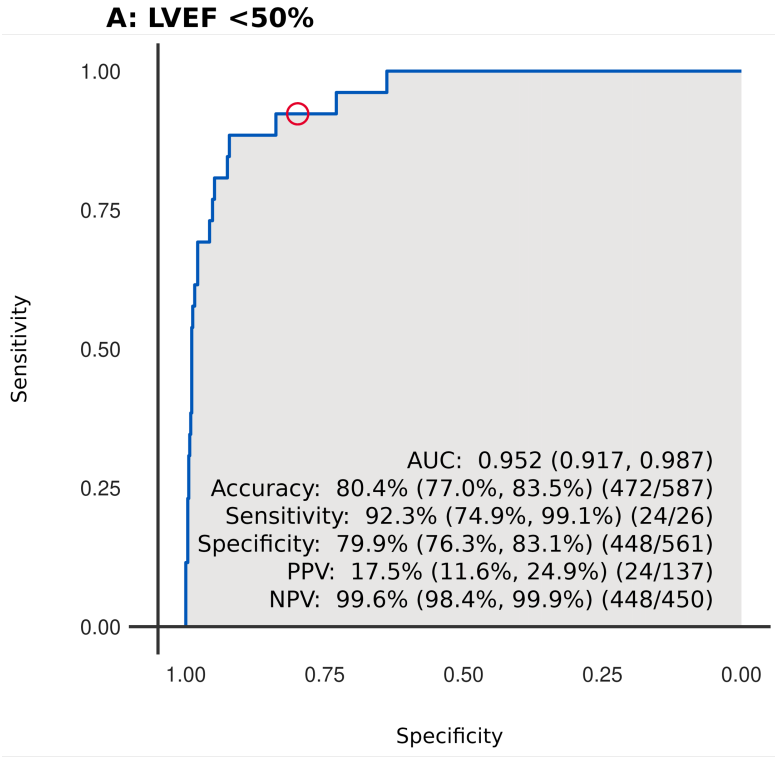


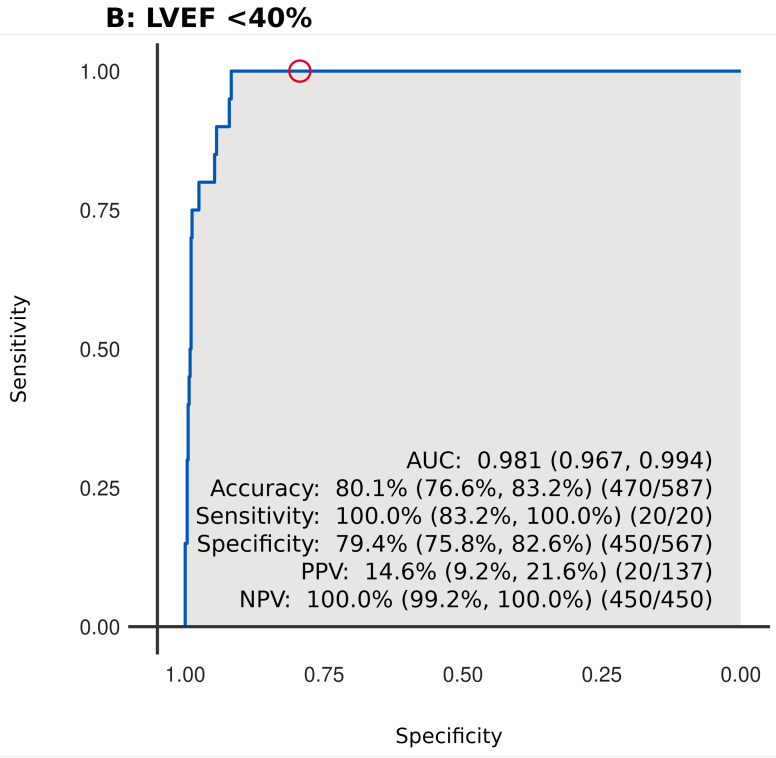

Odds ratio **2.3** (95% CI: 1.1, 4.8; p=**0.019**)

# RESULTS (Secondary)

In the intervention arm, the digital stethoscope had AUC values of

- 0.95 for detection of LVEF <50% and
- 0.98 for detection of LVEF <40%



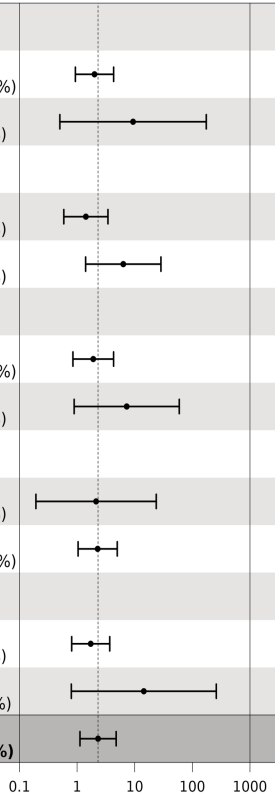
# RESULTS (Secondary)

Analysis performed to test for differential effects by strata.

We anticipated sparse data with stratification due to a low number of events overall.

The direction of the effect estimates were similar across strata

| Group | N | Overall | Control Arm | Intervention Arm | Odds Ratio |
|---|---|---|---|---|---|
| **Region** | | | | | *p=0.16* |
| Northern Nigeria | 395 | 31/395<br>7.8% (5.4%, 11.0%) | 11/202<br>5.4% (2.7%, 9.5%) | 20/193<br>10.4% (6.4%, 15.6%) | 2.0 (0.9, 4.3) |
| Southern Nigeria | 800 | 4/800<br>0.5% (0.1%, 1.3%) | 0/406<br>0.0% (0.0%, 0.9%) | 4/394<br>1.0% (0.3%, 2.6%) | 9.4 (0.5, 174.6) |
| **Age group** | | | | | *p=0.08* |
| <30 years | 521 | 21/521<br>4.0% (2.5%, 6.1%) | 9/267<br>3.4% (1.6%, 6.3%) | 12/254<br>4.7% (2.5%, 8.1%) | 1.4 (0.6, 3.4) |
| 30+ years | 674 | 14/674<br>2.1% (1.1%, 3.5%) | 2/341<br>0.6% (0.1%, 2.1%) | 12/333<br>3.6% (1.9%, 6.2%) | 6.3 (1.4, 28.5) |
| **Ethnicity** | | | | | *p=0.22* |
| Hausa | 337 | 27/337<br>8.0% (5.3%, 11.4%) | 10/174<br>5.7% (2.8%, 10.3%) | 17/163<br>10.4% (6.2%, 16.2%) | 1.9 (0.8, 4.3) |
| Other | 858 | 8/858<br>0.9% (0.4%, 1.8%) | 1/434<br>0.2% (0.0%, 1.3%) | 7/424<br>1.7% (0.7%, 3.4%) | 7.3 (0.9, 59.3) |
| **Status at Entry** | | | | | *p=0.96* |
| Pregnant | 874 | 3/874<br>0.3% (0.1%, 1.0%) | 1/451<br>0.2% (0.0%, 1.2%) | 2/423<br>0.5% (0.1%, 1.7%) | 2.1 (0.2, 23.7) |
| Postpartum | 321 | 32/321<br>10.0% (6.9%, 13.8%) | 10/157<br>6.4% (3.1%, 11.4%) | 22/164<br>13.4% (8.6%, 19.6%) | 2.3 (1.0, 5.0) |
| **HDP** | | | | | *p=0.07* |
| No | 1,052 | 29/1,052<br>2.8% (1.9%, 3.9%) | 11/536<br>2.1% (1.0%, 3.6%) | 18/516<br>3.5% (2.1%, 5.5%) | 1.7 (0.8, 3.7) |
| Yes | 143 | 6/143<br>4.2% (1.6%, 8.9%) | 0/72<br>0.0% (0.0%, 5.0%) | 6/71<br>8.5% (3.2%, 17.5%) | 14.4 (0.8, 260.4) |
| **Overall** | **1,195** | **35/1,195**<br>**2.9% (2.0%, 4.0%)** | **11/608**<br>**1.8% (0.9%, 3.2%)** | **24/587**<br>**4.1% (2.6%, 6.0%)** | **2.3 (1.1, 4.8)** |



# STRENGTHS

**Strengths/Advantages:**

- Pragmatic design, engaged staff, rapid accrual
- Large, prospective trial evaluating an AI intervention in an obstetric sample
- Use of a portable, battery-operated device
- Real-time AI results
- Validation of the AI-intervention in the intervention arm
- Enrollment of a predominantly Black, ethnically, and regionally diverse, obstetric population in Nigeria

# LIMITATIONS

## Limitations

- Pragmatic design – participants seen at teaching hospitals (cardiologist + echocardiography)
    - Cardiomyopathy prevalence at tertiary centers may not be reflective of the general obstetric patient population in Nigeria
- Selected cutpoint (LVEF <50%) did not match categorizations used at model derivation
    - Original model developed by Mayo Clinic was trained to detect LVEF ≤ 35% and then retrained using single leads to detect LVEF < 40% for use with the digital stethoscope

# CONCLUSION

1

AI-guided screening resulted in double the number of cardiomyopathy cases diagnosed (OR: 2.3) suggesting that up to half are likely undetected with usual care.

2

AI-guided screening using a digital stethoscope is effective for detection of left ventricular systolic dysfunction among pregnant and postpartum women (AUC 0.95, Sens 92%, Spec 80%)

3

This intervention has the potential to improve cardio-obstetric care by reducing delays in the diagnosis of a life-threatening but treatable condition.

# THANKS TO OUR STUDY TEAM

## Mayo Clinic Team

- Andrea Carolina Morales-Lara, MD
- Patrick W. Johnson, BS
- Hanna J. Sledge, BS
- Mikolaj Wieczorek, BS
- Itzhak Zachi Attia, PhD
- Xiaoxi Yao, PhD
- Sabrina D. Phillips, MD
- Mohamad H. Yamani, MD
- Carl H. Rose, MD
- Yvonne Butler Tobah, MD
- Emily E. Sharpe, MD
- Francisco Lopez-Jimenez, MD, MBA
- Paul A. Friedman, MD
- Peter A. Noseworthy, MD
- Rickey E. Carter, PhD
- Jennifer Dugan, BA
- Crosena Crosby

## Nigeria Team

- Sadiq Ringim, MBBS (RSSH)
- Abdullahi Habib, MBBS (RSSH)
- Sabiu M. Hamza, MBBS (RSSH)
- Mrs Asma'u Abdullahi (RSSH)
- Mrs. Rabi Musa (RSSH)
- Mr. Abubakar Ibrahim Aliyu (RSSH)
- Kehinde Ibiyemi, MBBS (UITH)
- James A. Ogunmodede, MBBS (UITH)
- Hadijat Olaide Raji, MBBS (UITH)
- Prof. Munir'deen A. Ijaiya (UITH)
- Dr. Abiodun Adeniran (UITH)
- Ms. Adeola Adedokun (UITH)
- Ms. Omowunmi Ishola (UITH)
- Olusoji Jagun, MBBS (OOUTH)
- Francisca Inofomoh, MBCHB (OOUTH)
- Adeolu Temitope, MBBS (OOUTH)
- Ms. Ajifola Temilola (OOUTH)
- Dr. Adedeji Adekolade (OOUTH)
- Okechukwu Ogah, MBBS (UCH)
- Gbolahan Obajimi, MBBS (UCH)
- Olugbenga Oluseun Saanu MBBS (UCH)
- Mr. Solomon Aborisade (UCH)
- Ms. Oluwatosin Makinde (UCH)
- Dr. Olanike Allison Orimolade (UCH)
- Ms. Victoria Ojo (UCH)
- Ms. Khadijat Adenike Olatunde (UCH)
- Mr. Salawu Taofeek Oladotun (UCH)
- Mr. Oluwaseun Alabi (UCH)
- Dr. Akinsola Teslim Sanusi (UCH)
- Dr. Temitope Azeez Olukunle (UCH)
- Ms Ifeoluwa Alabede (UCH)
- Kamilu Karaye, BMBCH (AKTH)
- Sule Gaya, MBBS (AKTH)
- Isiaka Alfa, MBBS (AKTH)
- Dr. Naser A Ishaq (AKTH)
- Mr. Yahaya Sa'ad (AKTH)
- Bosede Afolabi, MBBS (LUTH)
- Amam C. Mbakwem, MBBS (LUTH)
- Oyewole A. Kushimo, MBBS (LUTH)
- Ms. Damilola Onietan (lead study coordinator, LUTH)
- Ms. Rachel Quao (LUTH)
- Cynthia Yohanna, MBBS (UK)

# THANK YOU



#AHA23

adedinsewo.demilade@mayo.edu
@DemiladeMD
mayoclinic.org