Heart Failure with Preserved Ejection Fraction - What is new?

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www.kardiologie-graz.at  www.heart.lbg.ac.at
The Relationship Between Pressure and Volume
• News I: Pathophysiology
• News II: Diagnosis?
• News III: Therapy?
Ventricular Dysfunction
• Impaired relaxation
• Impaired filling
• Systolic Dysfunction

Atrial dysfunction

Autonomic dysfunction
Chronotropic incompetence

Vascular dysfunction
Vascular stiffening
Ventriculo-arterial coupling

Elevated blood pressure
Inadequate BP response to exercise
Pulmonary hypertension

Valvular disease
Dynamic mitral regurgitation

„Heart failure“ with preserved EF
„Heart failure“
with preserved EF

Lung Disease
COPD

Iron deficiency
and anemia

Renal dysfunction
Volume overload

Aging &
Deconditioning

Obesity &
Sarcopenia

Psychic Disorders
Depression
Heart failure with preserved EF

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- Impaired relaxation
- Impaired filling
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- Dynamic mitral regurgitation
• News I: Pathophysiology
• News II: Diagnosis?
• News III: Therapy?
Mega-Trial Approach: HF + “preserved EF”
Prevalence and Significance of Alterations in Cardiac Structure and Function in Patients With Heart Failure and a Preserved Ejection Fraction

Michael R. Zile, MD; John S. Gottdiener, MD; Scott J. Hetzel, MS; John J. McMurray, MD; Michel Komajda, MD; Robert McKelvie, MD; Catalin F. Baicu, PhD; Barry M. Massie, MD; Peter E. Carson, MD; for the I-PRESERVE Investigators

**Background**—The purpose of this study was to examine the prevalence of abnormalities in cardiac structure and function present in patients with heart failure and a preserved ejection fraction (HFPEF) and to determine whether these alterations in structure and function were associated with cardiovascular morbidity and mortality.

**Methods and Results**—The Irbesartan in HFPEF trial (I-PRESERVE) enrolled 4128 patients; echocardiographic determination of left ventricular (LV) volume, mass, left atrial (LA) size, systolic function, and diastolic function were made at baseline in 745 patients. The primary end point was death or protocol-specific cardiovascular hospitalization. A secondary end point was the composite of heart failure death or heart failure hospitalization. Associations between baseline structure and function and patient outcomes were examined using univariate and multivariable Cox proportional hazard analyses. In this substudy, LV hypertrophy or concentric remodeling was present in 59%, LA enlargement was present in 66%, and diastolic dysfunction was present in 69% of the patients. Multivariable analyses controlling for 7 clinical variables (including log N-terminal pro-B-type natriuretic peptide indicated that increased LV mass, mass/volume ratio, and LA size were independently associated with an increased risk of both primary and heart failure events (all \( P<0.05 \)).

**Conclusions**—Left ventricular hypertrophy or concentric remodeling, LA enlargement, and diastolic dysfunction were present in the majority of patients with HFPEF. Left ventricular mass and LA size were independently associated with an increased risk of morbidity and mortality. The presence of structural remodeling and diastolic dysfunction may be useful additions to diagnostic criteria and provide important prognostic insights in patients with HFPEF.

**Clinical Trial Registration Information**—http://www.clinicaltrials.gov. Unique identifier: NCT00095238. (Circulation. 2011;124:00-00.)

**Key Words:** heart failure ▪ echocardiography ▪ ventricular ejection fraction
Almost 50%: no structural LV Remodeling!
HFA/ESC Recommendations

How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology

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See page 2421 for the editorial comment on this article (doi:10.1093/eurheartj/ehm412)
HFA/ESC Recommendations: Diagnosis

1. Signs and/or Symptoms of Heart Failure

2. Preserved global systolic LV Function (EF>50%)

3. Indices of abnormal LV relaxation, filling, compliance or stiffness

4. BNP or NTproBNP
Diagnosis: Diastolic Heart Failure

HFA/ESC 2007
Paulus W et al.
Diagnosis: Diastolic Heart Failure

HFA/ESC 2007
Paulus W et al.
E/é and LVEDP

LV Filling Pressure (mmHg)

E/E' < 8   E/E' 8-15   E/E' > 15

Little et al.; Circulation 2009; 120: 802-809
Diagnosis: Diastolic Heart Failure

Change in Paradigms 2013:

• New Echo Techniques & Parameters (e.g., strain, torsion)

• Echo Stress test („Diastolic Stress Test“)!

• New Biomarkers: Subgroups, Response to Therapy (e.g., Galectin-3, ST2)
HFpEF – News 2013

• News I: Pathophysiology
• News II: Diagnosis?
• News III: Therapy?
Systolic Heart Failure: Therapy 2013

- NYHA I
  - ACE – Inhibitors
  - Beta-Blockers
  - MR Antagonists
  - Digitalis
  - Diuretics

- NYHA II
  - AT-1-Antagonists/Ivabradine
- NYHA III
- NYHA IV
Diastolic Heart Failure: Therapy 2013

NYHA I

NYHA II

NYHA III

NYHA IV

Diuretics?
Large Trials in HFPEF – no clear benefit

Redfield M, Circ Heart Fail 2012;5;653-659
Emerging Therapies

1. Pharmacological management
   - Ivabradine
   - PDE-5 Inhibition
   - Guanylate cyclase stimulation
   - Neprilysin Inhibition
   - MR antagonists

2. Interventions and Devices
   - Renal Denervation
   - Interatrial Shunting, Vagus/Baroreceptor stimulation

3. Physical activity and Exercise
Ivabradine – $I_f$ channel inhibition

Heart rate reduction by $I_f$-inhibition improves vascular stiffness and left ventricular systolic and diastolic function in a mouse model of heart failure with preserved ejection fraction

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Genetic mouse model of HFPEF (db/db)

Invasive hemodynamics with Ivabradine

Ivabradine improved diastolic function

Study CL2-16257-101

Effects of ivabradine versus placebo on cardiac function, exercise capacity, and neuroendocrine activation, in patients with Chronic Heart Failure and Preserved left ventricular Ejection Fraction

An 8-month, randomised double-blind, placebo controlled, international, multicentre study

Phase II
Primary objective

Ivabradine vs placebo on diastolic function, exercise capacity and neuroendocrine activation over an 8-month treatment period in patients with chronic HF-PEF

Primary endpoint

Co-primary endpoint based on echocardiography (E/e’), neuroendocrine activation (NT-proBNP) and six-minute walk test evaluated at 8 months

Secondary objectives

-To evaluate the effects of ivabradine compared to placebo on cardiac function and structural parameters, quality of life (KCCQ), NYHA classification and other biomarkers
-To evaluate the safety and tolerance profile of ivabradine compared to placebo

Start: May 2013!
Increasing cyclic GMP in HFPEF?
Insufficient soluble Guanylate Cyclase (sGC): an unmet mechanism in HFPEF

- Myocardial dysfunction
  - impaired relaxation, diastolic stiffening, energy wastage

- Endothelial dysfunction
  - disturbed endothelium-dependent vasotone regulation

Desai A S, American Heart Journal, December 2011
Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure With Preserved Ejection Fraction
A Randomized Clinical Trial

216 patients
Randomized, double blind, placebo-controlled
Sildenafil 3x20mg (12w), 3x60mg 12w)
EF>50%
Elevated NTproBNP
PEP: peak VO2

Redfield M, JAMA, 2013;309(12)
Outcomes after 24 weeks:

### Table 3. Primary, Secondary, and Safety End Points

<table>
<thead>
<tr>
<th>Primary end point</th>
<th>Placebo</th>
<th>Sildenafil</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in peak oxygen consumption at 24 wk, median (IQR), mL/kg/min</td>
<td>94 -0.20 (−0.70 to 1.00)</td>
<td>91 -0.2 (−1.70 to 1.11)</td>
<td>.90</td>
</tr>
<tr>
<td>Secondary end points</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical rank score, mean[^{a}]</td>
<td>94 95.8</td>
<td>95 94.2</td>
<td>.85</td>
</tr>
<tr>
<td>Change in 6-minute walk distance at 24 wk, median (IQR), m</td>
<td>95 15.0 (−26.0 to 45.0)</td>
<td>90 5.0 (−37.0 to 55.0)</td>
<td>.92</td>
</tr>
<tr>
<td>Change in peak oxygen consumption at 12 wk, median (IQR), mL/kg/min</td>
<td>96 0.03 (−1.10 to 0.67)</td>
<td>97 0.01 (−1.35 to 1.25)</td>
<td>.98</td>
</tr>
<tr>
<td>Change in 6-minute walk distance at 12 wk, median (IQR), m</td>
<td>96 18.0 (−14.5 to 48.0)</td>
<td>99 10.0 (−25.0 to 36.0)</td>
<td>.13</td>
</tr>
<tr>
<td>Components of clinical rank score at 24 wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, No. (%)</td>
<td>103 0</td>
<td>113 3 (3)</td>
<td>.25</td>
</tr>
<tr>
<td>Hospitalization for cardiovascular or renal cause, No. (%)</td>
<td>103 13 (13)</td>
<td>113 15 (13)</td>
<td>.89</td>
</tr>
<tr>
<td>Change in MLHFQ, median (IQR)</td>
<td>91 −8 (−21 to 5)</td>
<td>91 −8 (−19 to 0)</td>
<td>.44</td>
</tr>
<tr>
<td>Safety end points, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>103 78 (76)</td>
<td>113 90 (80)</td>
<td>.49</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>103 16 (16)</td>
<td>113 25 (22)</td>
<td>.22</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; MLHFQ, Minnesota Living with Heart Failure Questionnaire.

\[^{a}\]A mean value of 95 in each group is expected under the null hypothesis of no treatment effect.

\[^{b}\]Site investigator identified causes of death were sudden death (n = 1), progressive cardiorenal failure (n = 1), and noncardiovascular (n = 1).
Insufficient soluble Guanylate Cyclase (sGC): an unmet mechanism in HFPEF

**Myocardial dysfunction**
- impaired relaxation, diastolic stiffening, energy wastage

**Endothelial dysfunction**
- disturbed endothelium-dependent vasotone regulation

**Oxidative stress**
- Inflammation

**Pathways:**
- **ACE-I / ARB**
- **MRA**
- **RAAS**
- **β-Blockers**
- **β-adrenergic stimulation**
- **sGC**
- **cGMP**
- **sGC stimulators**

**Desai A S, American Heart Journal, December 2011**
Changes from baseline in cardiac index, heart rate, and MAP at 16 weeks

Cardiac index

Adjusted placebo-corrected difference: +0.36 L·min⁻¹·m⁻² (95% CI: 0.18 to 0.54)

P=0.0001

Heart rate

Adjusted placebo-corrected difference: −0.4 bpm (95% CI: −4.0 to 3.2)

P=0.83
**SOCRATES Study Program**: parallel phase IIb studies with once daily oral sGC stimulator (coming Fall 2013)

<table>
<thead>
<tr>
<th><strong>SOCRATES-REDUCED</strong></th>
<th><strong>SOCRATES-PRESERVED</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>HF with reduced EF (HFrEF)</td>
</tr>
<tr>
<td><strong>LVEF</strong></td>
<td>&lt;45%</td>
</tr>
<tr>
<td><strong>Medical need</strong></td>
<td>High event rates after hospitalization for HF despite standard treatment</td>
</tr>
<tr>
<td><strong>Evidence</strong></td>
<td>Well tolerated cardiac index increase at 16 weeks Riociguat added to standard therapy in systolic HF and sec. PH (LEPHT)</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Parallel conduct of two dose finding ph IIb studies, each with 5 parallel arms (2 low doses and 2 with uptitration to higher doses) in patients stabilized after hospitalization for worsening chronic HF</td>
</tr>
</tbody>
</table>
Neprilysin Inhibition – The PARAMOUNT Trial

The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial

Scott D Solomon, Michael Zile, Burkert Pieske, Adriaan Voors, Amil Shah, Elisabeth Kraigher-Krainer, Victor Shi, Toni Bransford, Madoka Takeuchi, Jianjian Gong, Martin Lefkowitz, Milton Packer, John JV McMurray, for the Prospective comparison of ARNI with ARB on Management Of heart failure with preserved ejection fraction (PARAMOUNT) Investigators*

Solomon S D, Lancet 2012;380:1387-95
LCZ696 – A First-in-Class Angiotensin Receptor Neprilysin Inhibitor

Natriuretic Peptide System

- pro-BNP
- BNP
- NT-pro BNP
- Neprilysin
- Inactive fragments

Vasodilation
- ↓ blood pressure
- ↓ sympathetic tone
- ↓ aldosterone levels
- ↓ fibrosis
- ↓ hypertrophy
Natriuresis/Diuresis

Heart Failure

- LCZ696
- AHU377
- LBQ657
- Valsartan

Renin Angiotensin System

- Angiotensinogen (liver secretion)
- Angiotensin I
- Angiotensin II
- AT₁ receptor

Vasoconstriction
- ↑ blood pressure
- ↑ sympathetic tone
- ↑ aldosterone
- ↑ fibrosis
- ↑ hypertrophy
**PARAMOUNT: Study Design**

**Primary objective**
NT pro-BNP reduction from baseline at 12 weeks

**Secondary objectives**
- Echocardiographic measures of diastolic function, left atrial size, LV size and function, PASP
- HF symptoms, Clinical composite assessment and Quality of life (KCCQ)
- Safety and tolerability

Baseline randomization visit and visit at end of 12 weeks of core study

Clinicaltrials.gov NCT00887588
Primary Endpoint: NT-proBNP at 12 Weeks

LCZ696/Valsartan: 0.77 (0.64, 0.92)  
\[P = 0.005\]

\[p = 0.063\]
Changes in Key Echocardiographic Measures

**Left Atrial Volume**
- **12 Weeks**
  - LCZ696: -6 ml
  - Valsartan: -4 ml
- **36 Weeks**
  - LCZ696: -3 ml
  - Valsartan: -2 ml

**Change in Left Atrial Volume (ml)**
- **Valsartan**: -2.0 ml
- **LCZ696**: -1.8 ml

**E/E’**
- **12 Weeks**
  - LCZ696: 1.2
  - Valsartan: 1.5
- **36 Weeks**
  - LCZ696: 1.0
  - Valsartan: 1.0

**Change in E/E’**
- **Valsartan**: 0.5
- **LCZ696**: 0.0

**Left Atrial Width**
- **12 weeks**
  - LCZ696: -0.05 cm
  - Valsartan: -0.1 cm
- **36 weeks**
  - LCZ696: -0.1 cm
  - Valsartan: -0.05 cm

**Change in LA Width (cm)**
- **Valsartan**: 0.07
- **LCZ696**: 0.03

**Lateral E’**
- **12 weeks**
  - LCZ696: 0.5 cm/s
  - Valsartan: 1.0 cm/s
- **36 weeks**
  - LCZ696: 0.5 cm/s
  - Valsartan: 0.5 cm/s

**Change in Lateral Mitral Annular Relaxation Velocity (E’) (cm/s)**
- **Valsartan**: 0.5
- **LCZ696**: 0.5

No Significant Changes in LV volumes, Ejection Fraction, or LV mass at 12 or 36 weeks
MR Receptor Antagonism – Aldo-DHF

Effect of Spironolactone on Diastolic Function and Exercise Capacity in Patients With Heart Failure With Preserved Ejection Fraction
The Aldo-DHF Randomized Controlled Trial

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Albrecht G. Schmidt, MD
Elisabeth Kraigher-Krainer, MD
Caterina Colantonio, MD
Wolfraam Kamke, MD
Andre Duvinge, MD
Raul Stahlemer, MD
Kathleen Durstewitz, MD
Markus Loeffler, MD
Hans-Dirk Dingen, MD
Carsten Tschöpe, MD
Christoph Herrmann-Lingen, MD
Martin Halle, MD
Gerd Hasenfuss, MD
Götz Gellrich, PhD
Burkert Pieske, MD
for the Aldo-DHF Investigators

Heart Failure (HF) with preserved ejection fraction (EF) accounts for more than 50% of the total HF population.1 Community-based cohort studies have shown that mortality rates are similar in HF with preserved EF compared with HF with reduced EF,2 but data from large clinical trials point toward a better outcome in HF with preserved EF. This may indicate that comorbidities that are typically excluded in trials may contribute to the poor prognosis in HF with preserved EF.1,4 Left ventricular diastolic dysfunction and adverse cardiac remodeling are considered major

Importance Diastolic heart failure (ie, heart failure with preserved ejection fraction) is a common condition without established therapy, and aldosterone stimulation may contribute to its progression.

Objective To assess the efficacy and safety of long-term aldosterone receptor blockade in heart failure with preserved ejection fraction. The primary objective was to determine whether spironolactone is superior to placebo in improving diastolic function and maximal exercise capacity in patients with heart failure with preserved ejection fraction.

Design and Setting The Aldo-DHF trial, a multicenter, prospective, randomized, double-blind, placebo-controlled trial conducted between March 2007 and April 2012 at 10 sites in Germany and Austria that included 424 ambulatory patients (mean age, 67 [SD, 8] years; 52% female) with chronic New York Heart Association class II or III heart failure, preserved left ventricular ejection fraction of 50% or greater, and evidence of diastolic dysfunction.

Intervention Patients were randomly assigned to receive 25 mg of spironolactone once daily (n=213) or matching placebo (n=209) with 12 months of follow-up.

Main Outcome Measures The equally ranked co-primary end points were changes in diastolic function (E/e′) on echocardiography and maximal exercise capacity (peak VO2) on cardiopulmonary exercise testing, both measured at 12 months.

Results Diastolic function (E/e′) decreased from 12.7 (SD, 3.6) to 12.1 (SD, 3.7) with spironolactone and increased from 12.8 (SD, 4.4) to 13.6 (SD, 4.3) with placebo (adjusted mean difference, −1.5 [95% CI, −2.0 to −0.9; P<0.001]). Peak VO2 did not significantly change with spironolactone vs placebo (from 16.3 [SD, 3.6] mL/min/kg to 16.8 [SD, 4.0] mL/min/kg vs 16.4 [SD, 3.5] mL/min/kg to 16.9 [SD, 4.4] mL/min/kg, respectively; adjusted mean difference, +0.1 mL/min/kg; 95% CI, −0.6 to +0.8 mL/min/kg; P=0.81). Spironolactone induced reverse remodeling (left ventricular mass index declined; difference, −6 g/m²; 95% CI, −10 to −1 g/m²; P=0.009) and improved neuroendocrine activation (N-terminal pro-brain-type natriuretic peptide geometric mean ratio, 0.86; 95% CI, 0.75-0.99; P=0.03) but did not improve heart failure symptoms or quality of life and slightly reduced 6-minute walking distance (<15 m; 95% CI, −27 to −2 m; P=0.03). Spironolactone also modestly increased serum potassium levels (0.2 mmol/L; 95% CI, 0.1 to +0.3; P<0.001) and decreased estimated glomerular filtration rate (−5 mL/min/1.73 m²; 95% CI, −8 to −3 mL/min/1.73 m²; P<0.001) without affecting hospitalizations.

Conclusions and Relevance In this randomized controlled trial, long-term aldosterone receptor blockade improved left ventricular diastolic function but did not affect maximal exercise capacity, patient symptoms, or quality of life in patients with heart failure with preserved ejection fraction. Whether the improved left ventricular function observed in the Aldo-DHF trial is of clinical significance requires further investigation in larger populations.

Trial Registration clinicaltrials.gov Identifier: ISRCTN04726526; Eudra-CT No: 2006-002605-31

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Aldo-DHF Study Design

Multicenter, randomised, placebo-controlled double-blind, two-armed parallel-group study

Equally ranked co-primary endpoints: Change in diastolic function (E/é) and maximal exercise capacity (peak VO₂) after 12 months for spironolactone compared to placebo.

Secondary endpoints: Changes in other echocardiographic measures of cardiac function and structure; Changes in other measures of exercise capacity; Neuroendocrine activation; HF symptoms; Quality of life; Safety and tolerability of study medication.
Primary endpoint - E/é

Spironolactone: 12.7±3.6 to 12.1±3.7
Placebo: 12.8±4.4 to 13.6±4.3

(P<0.001 for difference between groups)
Primary endpoint - peak VO$_2$

Spironolactone: 16.3±3.6 to 16.8±4.6mL/min/kg
Placebo: 16.4±3.5 to 16.9±4.4mL/min/kg

($P=0.67$ for difference between groups)

**Time since randomisation**

*Edelmann F,.. Pieske B. JAMA 2013; February 27, 2013-Vol 309, No.8*
Results for functional and structural reverse remodelling remained significant after adjusting for blood pressure effects.
TOPCAT: Trial Design

Desai A S, American Heart Journal, 2011

- AGE \( \geq 50 \) YRS
- EF \( \geq 45\% \) WITHIN 6 MONTHS
- HEART FAILURE SYMPTOMS AND SIGNS
- CONTROLLED SYSTOLIC BP (< 140 mm Hg)*
- SERUM K+ \( \leq 5.0 \) MMOL/L

**PLUS ONE OF THE FOLLOWING:**
- HF HOSPITALIZATION WITHIN 12 MONTHS
- BNP \( \geq 100 \) PG/ML
- N-TERMINAL PRO-BNP \( \geq 360 \) PG/ML

**RANDOMIZE**

<table>
<thead>
<tr>
<th>PLACEBO</th>
<th>SPIRONOLACTONE</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 MG</td>
<td>15 MG</td>
</tr>
</tbody>
</table>

**DOSE TITRATION (TARGET 30 MG)**
* Optional Titration to 45 mg at 4 mos

**COMPOSITE PRIMARY ENDPOINT**
CV death, Aborted cardiac arrest, Hospitalization for management of HF

\[ N=3500 \]

Week 0

Week 4

\[ \sim 3.25 \text{ yrs} \]
Emerging Therapies

1. Pharmacological management
   - Ivabradine
   - PDE-5 Inhibition
   - Guanylate cyclase stimulation
   - Neprilysin Inhibition
   - MR antagonists

2. Interventions and Devices
   - Renal Denervation
   - Interatrial Shunting

3. Physical activity and Exercise
Results: Exercise Capacity

Primary Endpoint: peak VO2

Maximum Workload

Edelmann F & Pieske B, JACC 2011;
Diastolic Function & LA remodeling

Change in E/é Ratio

Change in LA Volume Index

Training
Control

P<0.001

Training
Control

Change in E/e' ratio
Change in left atrial volume index [mL/m²]

***

***
1. 50% of HF patients have HFPEF

1. Pathophysiology/Etiology is complex and multifactorial, comorbidities can contribute

2. Diagnosis?: EF>50% + objective evidence of diastolic dysfunction. Biomarkers? Stress test?

1. General management: Loop diuretics, risk factor control
1. No established targeted therapy for HFPEF

2. New pharmacological approaches under investigation:
   - Ivabradine (Phase II: Start 2013)
   - Soluble Guanyllyte cyclase stimulation (Phase II: Start 2013)
   - Neprilysin inhibition (Phase III: Start 2013)
   - MR Antagonists (Phase III: Ongoing)

3. New devices and interventions

4. Physical activity and exercise training (Phase II: Ongoing)