Clinical and Quality of Life Outcomes Across the Spectrum of Baseline Kidney Function Insights from the ISCHEMIA and ISCHEMIA-CKD Trials

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On behalf of the ISCHEMIA/ISCHEMIA-CKD Research Group
Disclosures

- ISCHEMIA/ISCHEMIA-CKD trials were supported by grants from the NHLBI
- Devices used in the trial were donated by Abbott Vascular, Medtronic, St. Jude Medical, Volcano, and Omron Healthcare; medications were provided by Arbor Pharmaceuticals, AstraZeneca Pharmaceuticals, and Merck Sharp & Dohme.
CKD Patients are Under-Represented in Contemporary Revascularization vs. Medicine SIHD Trials

2007

![COURAGE](image)

eGFR <30: 16 Subjects

2009

![BARI 2D](image)

Subjects with serum Cr >2 mg/dl excluded

2012

FAME 2 Trial

Serum Cr >2 mg/dl: 20 subjects
Study Design

**ISCHEMIA**

- Stable Patient
  - Moderate or severe ischemia (determined by site; read by core lab)
  - Blinded CCTA
  - Core lab anatomy eligible?
    - NO → Screen failure
    - YES → RANDOMIZE

  - INVASIVE Strategy
    - OMT + Cath + Optimal Revascularization
  - CONSERVATIVE Strategy
    - OMT alone
    - Cath reserved for OMT failure

**ISCHEMIA CRD**

- Patients with moderate or severe ischemia and eGFR <30 or on dialysis
  - RANDOMIZE 1:1

  - INVASIVE Strategy
    - Optimal Medical Therapy + Cath + Optimal Revascularization (if suitable)
  - CONSERVATIVE Strategy
    - Optimal Medical Therapy alone
    - Cath and revascularization (if suitable) reserved for Optimal Medical Therapy failure

Primary Endpoint: Composite of Death or MI

Study Objectives

• Evaluate clinical and QoL outcomes across the spectrum of eGFR
• Evaluate the impact of treatment strategy on clinical and QoL outcomes across the spectrum of eGFR
Endpoints

Primary Endpoint
- Time to death or MI

Major Secondary Endpoints
- Time to Death, MI, Hospitalization for Unstable Angina, Heart Failure or Resuscitated Cardiac Arrest
- Quality of Life

Safety Outcomes
- Procedural complications
- Composite of initiation of dialysis or death
Randomized Participants

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
<th>Stage 5/Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=1889</td>
<td>N=2551</td>
<td>N=738</td>
<td>N=311</td>
<td>N=467</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>eGFR ≥ 90</th>
<th>90&gt; eGFR ≥ 60</th>
<th>60&gt; eGFR ≥ 30</th>
<th>30&gt; eGFR ≥ 15</th>
<th>eGFR &lt;15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or high function</td>
<td>Mildly reduced function</td>
<td>Moderately reduced function</td>
<td>Severely reduced function</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>
CKD Stages and Outcomes

**Primary Endpoint**
*(Death or MI)*

- Stage 1: 9.52
- Stage 2: 10.72
- Stage 3: 18.42
- Stage 4: 34.21
- Stage 5: 38.01

**Major Secondary Endpoint**
*(Death/MI/Hosp for UA, HF or RCA)*

- Stage 1: 10.84
- Stage 2: 12.19
- Stage 3: 21.03
- Stage 4: 36.34
- Stage 5: 40.88

Bars represent cumulative incidence rates and the black squares represent hazard ratio.

*P<0.001*
CKD Stages and Outcomes

All-Cause Death

Bars represent cumulative incidence rates and the black squares represent hazard ratios.

Myocardial Infarction

Bars represent cumulative incidence rates and the black squares represent hazard ratios.
CKD Stages: Procedural Complications and Bleeding

Data are for both INV/CON groups combined. Bleeding outcome for the duration of the trial.
CKD Stages: Heterogeneity of Treatment Effect

**Primary Endpoint**
(Death or MI)

- Overall: 0.99 (0.87, 1.13)
- CKD Stage 1: 1.10 (0.83, 1.45)
- CKD Stage 2: 0.94 (0.75, 1.17)
- CKD Stage 3: 0.91 (0.67, 1.25)
- CKD Stage 4: 1.33 (0.88, 2.01)
- CKD Stage 5: 0.88 (0.64, 1.20)

**P_interaction = 0.47**

**Major Secondary Endpoint**
(Death/MI/Hosp for UA, HF or RCA)

- Overall: 1.00 (0.89, 1.14)
- CKD Stage 1: 1.15 (0.89, 1.50)
- CKD Stage 2: 0.89 (0.72, 1.10)
- CKD Stage 3: 1.01 (0.75, 1.36)
- CKD Stage 4: 1.27 (0.85, 1.88)
- CKD Stage 5: 0.92 (0.68, 1.25)

**P_interaction = 0.41**
Heterogeneity of Treatment Effect as a Function of eGFR

Primary Endpoint
(Death or MI)

Major Secondary Endpoint
(Death/MI/Hosp for UA, HF or RCA)
CKD Stages: Heterogeneity of Treatment Effect

All-Cause Death

Favors INV

Favors CON

Myocardial Infarction

Favors INV

Favors CON

Overall

0.25 1 4

1.04 (0.87, 1.25)

0.91 (0.77, 1.08)

CKD Stage 1

1.11 (0.71, 1.71)

1.11 (0.79, 1.56)

CKD Stage 2

0.88 (0.62, 1.26)

0.94 (0.72, 1.22)

CKD Stage 3

1.26 (0.82, 1.94)

0.67 (0.44, 1.01)

CKD Stage 4

1.74 (1.08, 2.82)

0.78 (0.40, 1.54)

CKD Stage 5

0.78 (0.55, 1.12)

0.91 (0.57, 1.47)

P_{interaction} = 0.08

P_{interaction} = 0.46
**CKD Stages: Heterogeneity of Treatment Effect**

### Procedural MI

- **Overall**: 2.83 (1.83, 4.36)  
  - CKD Stage 1: 2.49 (1.10, 5.66)  
  - CKD Stage 2: 3.89 (1.99, 7.58)  
  - CKD Stage 3: 1.87 (0.64, 5.48)  
  - CKD Stage 4: 1.93 (0.18, 21.36)  
  - CKD Stage 5: 1.84 (0.44, 7.68)

- **P_interaction** = 0.74

### Non Procedural MI

- **Overall**: 0.68 (0.56, 0.83)  
  - CKD Stage 1: 0.79 (0.53, 1.17)  
  - CKD Stage 2: 0.63 (0.45, 0.88)  
  - CKD Stage 3: 0.59 (0.38, 0.93)  
  - CKD Stage 4: 0.61 (0.29, 1.30)  
  - CKD Stage 5: 0.82 (0.49, 1.37)

- **P_interaction** = 0.79
### CKD Stages: Heterogeneity of Treatment Effect

#### Stroke

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>Favors INV</th>
<th>Favors CON</th>
<th>( P_{\text{interaction}} = 0.08 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1.60 (1.09, 2.34)</td>
<td>( 2.09 (0.85, 5.14) )</td>
<td>( 0.86 (0.46, 1.61) )</td>
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<tr>
<td>CKD Stage 1</td>
<td></td>
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<tr>
<td>CKD Stage 5</td>
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#### Death or New Dialysis

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<tr>
<th>CKD Stage</th>
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<th>Favors CON</th>
<th>( P_{\text{interaction}} = 0.29 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1.15 (0.95, 1.38)</td>
<td>( 1.09 (0.70, 1.68) )</td>
<td>( 0.89 (0.62, 1.26) )</td>
</tr>
<tr>
<td>CKD Stage 1</td>
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<tr>
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</table>
SAQ-7 Summary Score as a Function of eGFR

Month 3

Month 12

Month 36

Score

Treatment Effect on Score

Estimated GFR
SAQ-7 Angina Frequency Score as a Function of eGFR

Month 3

Score

Month 12

Treatment Effect on Score

Month 36

Estimated GFR
SAQ-7 Angina Frequency Score at 12 months by Baseline Angina Frequency
Conclusions

• Exponential increase in cardiovascular events with lower kidney function
• Procedure related complications and bleeding increased with lower kidney function
• There was no evidence of meaningful heterogeneity of treatment effect for clinical outcomes across eGFR spectrum
  – No difference in INV vs. CON for primary or major secondary outcome
  – Increase in procedural MI but decrease in non procedural MI with INV
Conclusions

• Nominal heterogeneity of treatment effect such that there was
  – Increased risk of death with INV in those with CKD stage 4
  – Increased risk of stroke with INV in those with CKD stage 4/5

• Significant and durable benefit of INV at improving angina related QoL but the effect attenuated in those with less symptoms and at lower eGFR (below 30-45)