Disclosure

1. Consulting:
   1. Alere, Baxter, Gambro, Spectral Diagnostics, Otsuka

2. Speaking:
   1. Alere, Gambro, Otsuka
1. “Established AKI” in critical illness
   1. Few (if any) interventions
   2. Supportive

2. Many interventions require evidence:
   1. Better quality (i.e. randomized trials)
   2. More applicable
Background ~ Loop Diuretics

- Act in TAL LOH
- Inhibit Na–K–Cl carrier
- Compete with Cl site
- Reduce net re-absorption
  - Na, Cl, K, Mg, Ca
  - H2O
- Action dependent on delivery to site of action:
**Rationale for Loop Diuretics**

1. Direct renal vasodilator

3. Attenuate medullary hypoxia by inhibiting Na+/K+/2Cl− pump to reduce tubular O2 demand

5. Attenuate ischemic/reperfusion-induced apoptosis and associated gene transcription

7. Mitigate fluid overload/accumulation

Kramer et al KI 1980; Aravindan et al Ren Fail 2007; Aravindan et al Ren Fail 2006; Grams et al CJASN 2011
“Unload” the Stressed Kidney?

1. Acute renal failure = “acute renal success”

2. ↓ in GFR (mediated by TGF) = ↓ reabsorptive work
   1. Preserve renal O2 supply/demand + medullary oxygenation
   2. Mitigate ischemic/hypoxic injury

3. If protective – why do we apply strategies to ↑ GFR?

Differential effects of human atrial natriuretic peptide and furosemide on glomerular filtration rate and renal oxygen consumption in humans

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Furosemide</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output (L/min)</td>
<td>5.6</td>
<td>6.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>80.2</td>
<td>80.6</td>
<td>NS</td>
</tr>
<tr>
<td>Renal plasma flow (mL/min)</td>
<td>802</td>
<td>779</td>
<td>NS</td>
</tr>
<tr>
<td>GFR (mL/min)</td>
<td>89.1</td>
<td>78.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Na reabsorption (mmol/min)</td>
<td>12.0</td>
<td>7.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FeNa (%)</td>
<td>1.8</td>
<td>29.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urine flow (mL/min)</td>
<td>2.4</td>
<td>23.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVO2 consumption (mL/min)</td>
<td>11.1</td>
<td>7.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>O2 extraction (renal) (%)</td>
<td>10.5</td>
<td>8.5</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
Acute renal failure is NOT an “acute renal success”—a clinical study on the renal oxygen supply/demand relationship in acute kidney injury

Bengt Redfors, MD, PhD; Gudrun Bragadottir, MD; Johan Sellgren, MD, PhD; Kristina Swärd, MD, PhD; Sven-Erik Ricksten, MD, PhD

Per mmol Na reabsorbed: 1.9 mL O2 in AKI vs. 0.82 mL O2 in Control (2.4 x higher)
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Per mmol Na reabsorbed: 1.9 mL O2 in AKI vs. 0.82 mL O2 in Control (2.4 x higher)
Secondary retrospective analysis from the **Project to Improve Care in Acute Renal Disease (PICARD) database**:

- **Population**: 552 (64%) critically ill patients with AKI (defined as BUN > 40 mg/dL, sCr > 2 mg/dL or sustained rise > 1 mg/dL above baseline)

- **Intervention/Exposure**: Diuretic use at any time in 7 days following nephrology consultation

- **Outcome**: Death, non-recovery,
Diuretics were used in 59% (n=326)

<table>
<thead>
<tr>
<th>Diuretic Given on Day 1</th>
<th>n (%)</th>
<th>Dose (med)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>203 (62)</td>
<td>80 (20–320)</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>106 (58)</td>
<td>10 (2–29)</td>
</tr>
<tr>
<td>Metolazone</td>
<td>106 (33)</td>
<td>10 (5–20)</td>
</tr>
<tr>
<td>Hydrodiuril</td>
<td>13 (4)</td>
<td>–</td>
</tr>
<tr>
<td>Loop + Thiazide</td>
<td>105 (32)</td>
<td>–</td>
</tr>
<tr>
<td>Variable</td>
<td>Diuretic (n=226)</td>
<td>No Diuretic (n=326)</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>58.1 (17.1)</td>
<td>53.8 (18.0)</td>
</tr>
<tr>
<td>History of CHF (n, %)</td>
<td>87 (27)</td>
<td>30 (13)</td>
</tr>
<tr>
<td>Nephrotoxic (n, %)</td>
<td>61 (19)</td>
<td>28 (12)</td>
</tr>
<tr>
<td>Respiratory Failure (n, %)</td>
<td>241 (74)</td>
<td>143 (64)</td>
</tr>
<tr>
<td>Cardiac Failure (n, %)</td>
<td>148 (45)</td>
<td>75 (33)</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>61.6 (34.6)</td>
<td>72.3 (43.4)</td>
</tr>
<tr>
<td>sCr (mg/dl)</td>
<td>3.6 (1.9)</td>
<td>4.1 (3.3)</td>
</tr>
<tr>
<td>Variable</td>
<td>Crude OR (95% CI)</td>
<td>Adjusted OR (95% CI)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>In-Hospital Mortality</td>
<td>1.37 (0.97–1.92)</td>
<td>1.65 (1.05–2.58)</td>
</tr>
<tr>
<td>Non-Recovery</td>
<td>1.53 (1.08–2.15)</td>
<td>1.70 (1.14–2.53)</td>
</tr>
<tr>
<td>Composite</td>
<td>1.48 (1.02–2.12)</td>
<td>1.74 (1.12–2.68)</td>
</tr>
<tr>
<td>Composite (Ever/Never, n=416)</td>
<td>2.01 (1.26–3.20)</td>
<td>3.15 (1.74–5.62)</td>
</tr>
</tbody>
</table>
Furosemide dose-equivalent (mg/mL urine output/d) as surrogate for “diuretic responsiveness” – median 0.34 mg/mL

DE (dark circle) > 1.0 mg/mL – OR 2.94 (1.6–5.4)
DE (triangle) < 1.0 mg/mL – OR 1.15 (0.8–1.7)
Diuretics, Mortality, and Nonrecovery of Renal Function in Acute Renal Failure

Ravindra L. Mehta; Maria T. Pascual; Sharon Soroko; et al.


Day 1 Status
- No Diuretics
- Total Daily Furosemide Equivalent/Total Urine Output <1.0
- Total Daily Furosemide Equivalent/Total Urine Output ≥1.0
“The risk was borne largely by patients who were relatively unresponsive to diuretics”... and this
1. Secondary analysis of the *Beginning and Ending Support Therapy (BEST)* for the Kidney database:

1. **Population:** 1,731 critically ill patients with AKI (defined by: need for RRT; BUN > 86 mg/dL, K > 6.5 mmol/L; oliguria < 200 mL/12 hr; anuria)

2. **Intervention/Exposure:** Diuretic use after study enrolment

3. **Outcome:** In-hospital death
**Diuretics and mortality in acute renal failure**

Shigehiko Uchino, MD; Gordon S. Doig, PhD; Rinaldo Bellomo, MD; Hiroshi Morimatsu, MD; Stanislaw Morgera, MD; Miet Schetz, MD; Ian Tan, MD; Catherine Bouman, MD; Ettiene Macedo, MD; Noel Gibney, MD; Ashita Tolwani, MD; Claudio Ronco, MD; John A. Kellum, MD; for the Beginning and Ending Supportive Therapy for the Kidney (B.E.S.T. Kidney) Investigators

<table>
<thead>
<tr>
<th>Diuretic Use</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diuretic use</td>
<td>1,117 (60.8)</td>
</tr>
<tr>
<td>Furosemide</td>
<td>1,098 (98.3)</td>
</tr>
<tr>
<td>Other loop diuretic</td>
<td>29 (2.6)</td>
</tr>
<tr>
<td>Mannitol</td>
<td>22 (2.0)</td>
</tr>
<tr>
<td>Metolazone</td>
<td>19 (1.7)</td>
</tr>
<tr>
<td>Spirolactone</td>
<td>18 (1.6)</td>
</tr>
<tr>
<td>Thiazides</td>
<td>14 (1.3)</td>
</tr>
<tr>
<td>Other</td>
<td>14 (1.3)</td>
</tr>
</tbody>
</table>
# Diuretics and mortality in acute renal failure

Shigeiko Uchino, MD; Gordon S. Doig, PhD; Rinaldo Bellomo, MD; Hiroshi Morimatsu, MD; Stanislaw Morgera, MD; Miet Schetz, MD; Ian Tan, MD; Catherine Bouman, MD; Etiene Macedo, MD; Noel Gibney, MD; Ashita Tolwani, MD; Claudio Ronco, MD; John A. Kellum, MD; for the Beginning and Ending Supportive Therapy for the Kidney (B.E.S.T. Kidney) Investigators

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diuretic (n=1,117)</th>
<th>No Diuretic (n=626)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of ICU stay</td>
<td>11 (5–22)</td>
<td>9 (4–20)</td>
</tr>
<tr>
<td>Length of Hospital stay</td>
<td>23 (12–45)</td>
<td>21 (9–44)</td>
</tr>
<tr>
<td>ICU Mortality (%)</td>
<td>53.4</td>
<td>48.2</td>
</tr>
<tr>
<td>Hospital Mortality (%)*</td>
<td>62.4</td>
<td>57.1</td>
</tr>
<tr>
<td>Discharge Dialysis</td>
<td>32.7</td>
<td>38.2</td>
</tr>
</tbody>
</table>
Diuretics and mortality in acute renal failure*

Shigehiko Uchino, MD; Gordon S. Doig, PhD; Rinaldo Bellomo, MD; Hiroshi Morimatsu, MD; Stanislao Morgera, MD; Miet Schetz, MD; Ian Tan, MD; Catherine Bouman, MD; Etienne Macedo, MD; Noel Gibney, MD; Ashita Tolwani, MD; Claudio Ronco, MD; John A. Kellum, MD; for the Beginning and Ending Supportive Therapy for the Kidney (B.E.S.T. Kidney) Investigators

<table>
<thead>
<tr>
<th>In-Hospital Mortality</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1 (Mehta et al)</td>
<td>1.21</td>
</tr>
<tr>
<td></td>
<td>(0.96–1.50)</td>
</tr>
<tr>
<td>Model 2 (Propensity)</td>
<td>1.22</td>
</tr>
<tr>
<td></td>
<td>(0.91–1.60)</td>
</tr>
<tr>
<td>Model 3 (Multi-collinearity)</td>
<td>1.22</td>
</tr>
<tr>
<td></td>
<td>(0.92–1.60)</td>
</tr>
</tbody>
</table>
PICARD/BEST Studies

1. Caveats to consider to these studies:
   1. Observational $\rightarrow$ Confounding
   2. Selection/information bias
   3. Severe/advanced AKI at inclusion (sCr>3.5)*
   4. No data on specifics of fluid resuscitation
   5. No data on fluid overload/accumulation
   6. No data on timing of diuretic use
Loop diuretics in the management of acute renal failure: a systematic review and meta-analysis

Sean M Bagshaw, Anthony Delaney, Michael Haase, William A Ghali and Rinaldo Bellomo

Citations identified and screened for retrieval: 1336

Citations deemed not relevant and excluded: 1274

Potentially relevant citations identified for further review: 62

Citations excluded: 57
- 31 No randomisation
- 8 No control group
- 8 Review articles
- 5 No acute renal failure
- 2 Editorials
- 2 Duplicate publication
- 1 Animal study

RCTs included in final analysis: 5
Loop diuretics in the management of acute renal failure: a systematic review and meta-analysis

Sean M Bagshaw, Anthony Delaney, Michael Haase, William A Ghali and Rinaldo Bellomo

Figure 2. Forest plot for mortality associated with loop diuretics compared with control from four randomised controlled trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cantarovich (1971)</td>
<td>0.68 (0.19 – 2.44)</td>
<td>10.9%</td>
</tr>
<tr>
<td>Kleinknecht (1976)</td>
<td>1.14 (0.42 – 3.08)</td>
<td>14.0%</td>
</tr>
<tr>
<td>Shilliday (1997)</td>
<td>2.10 (0.86 – 5.12)</td>
<td>12.6%</td>
</tr>
<tr>
<td>Cantarovich (2004)</td>
<td>1.26 (0.79 – 1.99)</td>
<td>62.5%</td>
</tr>
<tr>
<td>Overall</td>
<td>1.28 (0.89 – 1.84)</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Figure 3. Forest plot for urine output associated with loop diuretics compared with control from three randomised controlled trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cantarovich (1971)</td>
<td>1.57 (0.43 – 5.75)</td>
<td>29.7%</td>
</tr>
<tr>
<td>Kleinknecht (1976)</td>
<td>1.96 (0.62 – 6.21)</td>
<td>34.8%</td>
</tr>
<tr>
<td>Shilliday (1997)</td>
<td>3.99 (1.49 – 10.66)</td>
<td>35.5%</td>
</tr>
<tr>
<td>Overall</td>
<td>2.56 (1.35 – 4.85)</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
The efficacy of loop diuretics in acute renal failure: Assessment using Bayesian evidence synthesis techniques

Sriram Sampath, MD (Gen Med); John L. Moran, FRACP, FJFICM, MD; Petra L. Graham, PhD; Sue Rockliff, BA, Grad Dip Lib; Andrew D. Bersten, MD, FANZCA, FJFICM; Keith R. Abrams, PhD

Mortality

Diuretic Beneficial

Non-randomised
Bercziade (1969)
Cantarovich (1973)
Chandra (1975)
Minuth (1976)
Sorriakghanyavat (1978)
Lumbertgul (1989)
Mehta (2002)
Uchino (2004)

Overall - non-randomised

Randomised
Cantarovich (1971)
Kleinknecht (1976)
Brown (1981)
Shillingford (1997)
Cantarovich (2004)

Overall - randomised

Overall

Diuretic Harmful

Risk ratio (95% CI)

Non-randomised
1.08 (0.68, 1.34)
1.07 (0.73, 1.27)
1.08 (0.72, 1.37)
1.11 (0.90, 1.45)
1.10 (0.76, 1.51)
1.10 (0.75, 1.50)
1.12 (0.99, 1.30)
1.10 (1.02, 1.18)
1.09 (0.91 to 1.25)

Randomised
1.09 (0.73, 1.40)
1.12 (0.81, 1.49)
1.12 (0.86, 1.45)
1.16 (0.93, 1.58)
1.13 (0.92, 1.42)

Overall - randomised
1.12 (0.92 to 1.35)

Overall
1.10 (0.85 to 1.42)
The efficacy of loop diuretics in acute renal failure: Assessment using Bayesian evidence synthesis techniques

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**Time to Normalize SCr/Urea**

Diuretics take less time  
Non-randomised
- Cantarovitch (1973)
- Borirakchanyevat (1978)
- Lumlertgul (1989)

Overall - non-randomised  
- Mean difference (95% CI)  
  - Mean difference  
  - -2.47 (-8.03, 1.21)  
  - -2.47 (-8.03, 1.21)

Diuretics take more time
Randomised
- Cantarovitch (1971)
- Kleinknecht (1976)
- Brown (1981)
- Shilliday (1997)
- Cantarovitch (2004)

Overall - randomised  
- Mean difference (95% CI)  
  - Mean difference  
  - -2.49 (-7.24, 0.64)  
  - -2.49 (-7.24, 0.64)

Overall  
- Mean difference (95% CI)  
  - Mean difference  
  - -1.54 (-5.62 to 2.45)  
  - -1.54 (-5.62 to 2.45)
The efficacy of loop diuretics in acute renal failure: Assessment using Bayesian evidence synthesis techniques

Sriram Sampath, MD (Gen Med); John L. Moran, FRACP, FJFICM, MD; Petra L. Graham, PhD; Sue Rockliff, BA, Grad Dip Lib; Andrew D. Bersten, MD, FANZCA, FJFICM; Keith R. Abrams, PhD

Rate of Initiation of RRT

Diuretics Beneficial  Diuretics Harmful

Non-randomised

Cantarovic (1973)  0.56 (0.45, 0.68)
Lunertgul (1989)  0.66 (0.38, 1.58)

Overall - non-randomised  0.66 (0.45 to 1.03)

Randomised

Cantarovic (1971)  0.59 (0.46, 0.76)
Kleinknecht (1976)  0.67 (0.69, 1.10)
Brown (1981)  0.83 (0.63, 1.11)
Cantarovic (2006)  0.93 (0.96, 1.02)

Overall - randomised  0.76 (0.53 to 1.00)

Overall  0.71 (0.47 to 1.06)

Incidence rate ratio (IRR)
The efficacy of loop diuretics in acute renal failure: Assessment using Bayesian evidence synthesis techniques

Time to Achieve Diuresis >1500mL/day

Diuretics take less time

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cantarovich (1971)</td>
<td>-9.10 (-12.54, -5.83)</td>
</tr>
<tr>
<td>Chandra (1975)</td>
<td>-8.72 (-13.46, -4.02)</td>
</tr>
<tr>
<td>Overall - non-randomised</td>
<td>-8.28 (-12.62 to -3.08)</td>
</tr>
<tr>
<td>Cantarovich (1971)</td>
<td>-8.24 (-12.15, -4.40)</td>
</tr>
<tr>
<td>Kleinknecht (1976)</td>
<td>-4.61 (-7.53, -1.66)</td>
</tr>
<tr>
<td>Brown (1981)</td>
<td>-12.38 (-15.74, -9.04)</td>
</tr>
<tr>
<td>Cantarovich (2004)</td>
<td>-2.22 (-3.59, -0.86)</td>
</tr>
<tr>
<td>Overall - randomised</td>
<td>-7.44 (-11.94 to -2.74)</td>
</tr>
<tr>
<td>Overall</td>
<td>-7.70 (-12.51 to -2.91)</td>
</tr>
</tbody>
</table>
Data generated from these trials:
1. Low quality/reporting
2. Single centre/small
3. Co-interventions (dopamine, mannitol)
4. Not all were critically ill
5. Prolonged periods of oligo-anuria
6. Already receiving RRT
7. High-dose bolus
8. No titration to physiologic end-points
1. Questionable internal validity
3. Limited applicability to modern ICU practice
5. Low generalizability
Diuretics in the Management of Acute Kidney Injury: A Multinational Survey

Sean M. Bagshaw\textsuperscript{a}, Anthony Delaney\textsuperscript{b,c}, Daryl Jones\textsuperscript{d}, Claudio Ronco\textsuperscript{f}, Rinaldo Bellomo\textsuperscript{a,e}
Comparison of Two Fluid-Management Strategies in Acute Lung Injury

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*

<table>
<thead>
<tr>
<th>Variable</th>
<th>CON</th>
<th>LIB</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (day 60) (%)</td>
<td>25.5</td>
<td>28.4</td>
<td>0.30</td>
</tr>
<tr>
<td>Ventilator-free days (d 1–28)</td>
<td>14.6</td>
<td>12.1</td>
<td>0.001</td>
</tr>
<tr>
<td>ICU-free days (d 1–28)</td>
<td>13.4</td>
<td>11.2</td>
<td>0.001</td>
</tr>
<tr>
<td>RRT (day 60) (%)</td>
<td>10</td>
<td>14</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*Figure 3. Probability of Survival to Hospital Discharge and of Breathing without Assistance during the First 60 Days after Randomization.*
Fluid balance (per L/day) on 60-day mortality
OR 1.61 (95% CI, 1.32–19.6, p<0.001)

CONSERVATIVE GROUP
1. Less fluid!
2. 0.9L vs. 2.2L per day, p<0.001
3. 6.0L vs. 10.2L 6-day cumulative, p<0.001
Fluid Balance, Diuretic Use, and Mortality in Acute Kidney Injury

Morgan E. Grams,† Michelle M. Estrella,‡ Josef Coresh,‡‡, Roy G. Brower,* and Kathleen D. Liu§ for the National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network

CONSERVATIVE GROUP

1. More furosemide!
2. 80 mg vs. 23 mg per day, p<0.001
3. 562 mg vs. 159 mg 6-day cumulative,

Furosemide (per 100mg/d) on 60–d mortality OR 0.48 (95% CI, 0.28–0.81, p=0.007)
Furosemide does not improve renal recovery after hemofiltration for acute renal failure in critically ill patients: A double blind randomized controlled trial*

Peter H. J. van der Voort, MD, PhD, MSc; E. Christiaan Boerma, MD; Matty Koopmans, RN; Mariët Zandberg, MD; Joke de Ruiter, MD; Rik T. Gerritsen, MD; Peter H. M. Egbers, MD; W. Peter Kingma, MD; Michaël A. Kuiper, MD, PhD, FCCP, FCCM

Iso-volemic furosemide infusion (0.5 mg/kg/h) vs. placebo

<table>
<thead>
<tr>
<th></th>
<th>FUR (n=36)</th>
<th>PLAC (n=35)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Output (mL/hr)</td>
<td>247</td>
<td>117</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Urine [Na] (mmol/L)</td>
<td>73</td>
<td>37</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Recovery (%)</td>
<td>69.4</td>
<td>77.1</td>
<td>0.5</td>
</tr>
</tbody>
</table>
The SPARK Study: A randomized controlled trial of furosemide in critically ill patients with early acute kidney injury

ClinicalTrials.gov Identifier: NCT00978354
Principle Objectives:

1. **Efficacy**: in the primary outcome of progression in severity of kidney injury, defined as worsening RIFLE category AND/OR initiation of RRT;

2. **Safety**: in terms of potential adverse events associated with (attributed to) furosemide or placebo;

3. **Feasible**: in recruitment of eligible patients,
Secondary Clinical Objectives:

1. Fluid balance, electrolyte and acid–base homeostasis
2. Duration of AKI
3. Initiation of renal replacement therapy
4. Composite of major adverse kidney events

[MAKE] ~

1. Recovery of kidney function AND/OR
2. New or worse chronic kidney disease (CKD) AND/
1. Furosemide use is common in AKI
3. Data is conflicting on its efficacy
5. There is misalignment between evidence and clinical practice
7. There is equipoise for a randomized trial
9. The SPARK Study proposes to generate higher quality data to guide on this issue
Thank You For Your Attention!

Questions?

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