A Paradigm Shift in Contrast-Induced Acute Kidney Injury (CI-AKI) Prevention
Clinical Problem
Contrast viscosity increases 50X in kidney. Impedes filtration, delivery of $O_2$, & contrast excretion

Toxic to nephrons

Combination impedes kidney function and kills nephrons

Takes up to 5 days to flush contrast unaided

Fähling et al. Nature Reviews | Nephrology 2017
CI-AKI Significantly Increases Risk of Dialysis & Mortality

- CI-AKI drastically increases the risk of:
  - Serious cardiac and renal diseases
  - Worse outcomes from cardiac and renal diseases
  - Acute and chronic dialysis
- CI-AKI causes immediate and irreversible loss of nephrons, leading to long-term decline in kidney function

Mortality Rate

<table>
<thead>
<tr>
<th></th>
<th>CI-AKI</th>
<th>No CI-AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-Hospital</td>
<td>15%</td>
<td>5%</td>
</tr>
<tr>
<td>1-Year</td>
<td>19%</td>
<td>19%</td>
</tr>
<tr>
<td>30-Day 1-Year</td>
<td>16%</td>
<td>1%</td>
</tr>
<tr>
<td>1-Year</td>
<td>23%</td>
<td>3%</td>
</tr>
<tr>
<td>In-Hospital 1-Year</td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td>5-Year 1-Year</td>
<td>23%</td>
<td>7%</td>
</tr>
<tr>
<td>2-Year</td>
<td>40%</td>
<td>12%</td>
</tr>
<tr>
<td>5-Year</td>
<td>90%</td>
<td>32%</td>
</tr>
</tbody>
</table>

30K
Estimated CI-AKI 1-year mortality in US/EU

13x
Increased 30-day mortality risk due to CI-AKI

15x
Increased major adverse cardiac event rate due to CI-AKI

Withholding Catheterization Not the Answer

- In a review of matched group of Medicare patients with cardiac diagnosis, 25% of patients with chronic kidney disease (CKD) received catheterization, compared to 47% of patients with similar cardiac diagnosis without CKD.

- This “Renalism”, resulted in one year mortality for CKD patients who did not receive angiography of 60%, compared to 30% mortality for patients who did receive angiography.

- In many cases, patient is still better off receiving catheterization than not.

- Often, CKD patients have worsened cardiac disease due to their renal dysfunction.

1 Year Mortality for CKD Patients with Similar Cardiac Diagnosis

Need a solution that allows patients with poor renal function and cardiac disease to safely undergo procedures using contrast.

Economic Cost
Economic Cost
€4.3B In Direct CI-AKI Cath Lab Costs (€ 2.1B US/ € 2.2B EU)

Mix by Procedure

- **Coronary Angiogram (CA)**: 45%
- **Percutaneous Coronary Intervention (PCI)**: 29%
- **Peripheral Vascular Intervention (PVI)**: 2%
- **Transcatheter Aortic Valve Replacement (TAVR)**: 4%
- **Endovascular Aneurysm Repair (EVAR)**: 20%

$10K
Average per-patient cost resulting from CI-AKI

3.75
Additional hospital days due to CI-AKI

1.6MM
Hospital days in US and EU resulting from CI-AKI

CI-AKI Leads to Massive Long-Term Dialysis Costs

**CI-AKI Chronic Dialysis Cost**

- **€ 3.8B**

- **19K**
  - Cases of acute dialysis in EU/US related to CI-AKI (75% lead to chronic dialysis)

- **€ 899K**
  - Average annual cost of chronic dialysis

- **3**
  - Years spent on average on chronic dialysis

**CI-AKI results in additional indirect costs incurred from:**

- Chronic Dialysis
- Renalism¹
- Major Adverse Cardiac Events
- Palliative Care
- Worse outcomes from Adverse Cardiac and Renal Events
- Opportunity costs to providers from over-utilization
- PR costs due to decline in brand/reputation
- Malpractice costs (litigation)
- Opportunity costs to society from CI-AKI and related hospitalizations

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RenalGuard matches fluid in- and out-flows through automated saline infusion
- Achieves previously infeasible urine rates shown to protect kidneys
- Eliminates danger of over- or under-hydration
- Infuses saline after diuretic administration and urination

Requires minimal nurse intervention

No interference with cath operation

RenalGuard results in:
- Lower concentration of contrast
- Faster elimination of contrast
- Decrease in kidney oxygen demand
- Increase in kidney oxygen supply
RenalGuard: Only Solution Addressing All Fundamental Causes of CI-AKI

- Contrast viscosity increases 50X in kidney. Impedes filtration, delivery of O₂, & contrast excretion
- Toxic to nephrons
- Combination impedes kidney function and kills nephrons
- Takes up to 5 days to flush contrast unaided
RenalGuard and Urine Rate Output

Range of Urine Output Response

RenalGuard and Urine Rate Output

Urine Rate (mL/hour)

0 200 400 600 800 1000

0:30 1:00 2:00 3:00 4:00 5:00 6:00 7:00 8:00 9:00 10:00

Time since RG (h:mm)

Clinical Studies
Consistently Positive Outcomes across 1455 Patients studied

CI-AKI Incidence in Prospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Standard of Care</th>
<th>RenalGuard</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYTHOS</td>
<td>18.0%</td>
<td>-74%</td>
</tr>
<tr>
<td>REMEDIAL II</td>
<td>13.0%</td>
<td>-79%</td>
</tr>
<tr>
<td>AKIGUARD</td>
<td>25.0%</td>
<td>7.0%</td>
</tr>
<tr>
<td>PROTECT-TAVI</td>
<td>25.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>CI-AKI &amp; TAVI</td>
<td>39.0%</td>
<td>-88%</td>
</tr>
</tbody>
</table>

Weighted Average Decrease of CI-AKI using RenalGuard in Prospective Studies

77%
PROTECT-TAVI

- CI-AKI strong predictor of 1-year mortality (One study: 47.9% vs. 15.7%)
- TAVI Patients without AKI actually see GFR increase
- PROTECT-TAVI results project 27% reduction in 1-year mortality

<table>
<thead>
<tr>
<th>CI-AKI</th>
<th>Stage 3 CI-AKI</th>
<th>CI-AKI if eGFR &gt; 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>25%</td>
<td>1.8%</td>
<td>18%</td>
</tr>
<tr>
<td>5%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

P=0.014

n=112, randomized

No CI-AKI in patients without pre-existing kidney dysfunction

Barbanti PROTECT-TAVI JACC: Cardiovascular Interventions 2015.
Physician Feedback

“Our experience with RenalGuard has been very positive... RenalGuard has become the Standard of Care for at-risk patients at our center.”

Professor Shmuel Banai, MD - KOL
Director of Interventional Cardiology, Tel Aviv Sourasky Medical Center
Associate Professor of Cardiology, Hebrew University of Jerusalem
Author of 150 peer-reviewed publications

“RenalGuard has performed very nicely in a difficult patient population.”

Professor Antonio Bartorelli, MD – KOL, INVESTOR
Associate Professor of Cardiology, University of Milan
Head Coordinator of Invasive Cardiology, Monzino Cardiology Center
Fellow of European Society of Cardiology
Fellow of American College of Cardiology
Author of 135 peer-reviewed publications

How integrated is RenalGuard into your cath lab?
“All of the nurses in the CCU, ICU, cath lab, and the ward know how to set up the system and connect it to the patient. It’s a routine treatment now.”

Professor Vaikom Mahadevan, MD – KOL
Associate Professor of Medicine, University of California, San Francisco
Ex-Director of Adult Congenital Heart Disease (ACHD) and Transcatheter Aortic Valve Replacement (TAVR) Program, Manchester Royal Infirmary
Founder, Ex-Director of ACHD Interventional Program, NW England
Author of 56 peer-reviewed publications

What did it take to get RenalGuard integrated?
“The nurses train each other to operate the system. They love it - it’s very simple to operate, much easier than bringing patients in for overnight hydration, and they love seeing its impact on reducing adverse events for patients.”
Without effective CI-AKI prevention solutions, clinicians often reduce CM exposure by purposefully avoiding normal cath procedure when treating high-risk patients.

Cath avoidance dramatically increases Major Cardiac Events, Mortality, and other adverse outcomes relative to normal cath procedure.

**Competitive Advantage**

- Procedure Avoidance to Prevent CI-AKI Leads to Poor Outcomes

- Increases Adverse Events
  - Reduce Duration of Intervention
  - Reduce Amount of Intervention (treat only most stenosed lesions)
  - Stage Intervention Across Multiple Procedures
  - Completely Avoid Intervention “Renalism”

**RenalGuard Treats “Renalism”**

- Capture Cost Savings and Quality Revenue

- Addressable CKD patients Without RenalGuard
- CKD Patients With RenalGuard

- Drive Caths

**100% increase**
## Recommendations

| Patients with moderate-to-severe Chronic Kidney Disease |

Furosemide with **matched hydration** may be considered over standard hydration in patients at very high risk for CI-AKI or in cases where prophylactic hydration before the procedure cannot be accomplished.

| Dose |

Initial intravenous bolus of normal saline over 30 min followed by an i.v. Bolus of furosemide. Hydration infusion rate has to be adjusted to replace the patient’s urine output. When the rate of urine output is >300 mL/h, patients undergo the coronary procedure.

**Matched fluid replacement** maintained during the procedure and for 4 hours post-treatment.

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Cost Savings
AKIGUARD Indicates RenalGuard Cost Savings Extend beyond CI-AKI

n=133, randomized

- CI-AKI
  - 25% decrease
  - P=0.01

- MACCE in 12 months
  - 72% decrease
  - P<0.01

- eGFR decrease in 3 months
  - 100% decrease
  - P<0.01

- Hospital days in 12 months
  - 80% decrease
  - P=0.01

MACCE- Major cardiac or cerebrovascular events

AKIGUARD Indicates RenalGuard Cost Savings Extend beyond CI-AKI

Approximate Cost Savings

RenalGuard Cost

<€500

€6500

3.9
Reduction in hospital days out to 12 months

€1800
Approx. daily hospital cost

1300%
ROI

Benefits to Cath Lab and Hospital

- **Increase Overall Cath Volume:** Allow high-risk CKD patients who would otherwise not receive cath due to concerns about renal damage, expanding high-risk market by up to 100%.

- **Increase per-patient revenue:** Many payers reimburse at a higher rate for patients at high risk for CI-AKI.

- **Increase utilization of high-risk procedures:** Enables more CKD patients to be treated with advanced procedures, such as TAVI, CTO, and complex PCI.

- **Competitive Advantage and Differentiation:** Allows hospitals to become centers of excellence for treatment of CKD patients, increasing the lab’s overall referral base.

- **Cost Savings, Quality Revenue:** Reduced adverse events reduces costs and improves quality and clinical reputation.
Improved cardiac care: RenalGuard allows patients with advanced CKD to receive optimal cardiac care while reducing risk of AKI.

Reduced adverse events and re-admission: Results of AKIGUARD suggest significant potential for reduction in costly adverse events and re-admission.

Reduce progression to end stage renal disease (ESRD): Improved cardiac care should improve renal function and prevent deterioration of high-risk patients under management into dialysis.

Higher quality, lower costs: Reduction in dialysis population under management allows more competitive pricing of new high-risk patients, potentially providing a competitive advantage relative to other integrated care networks.
RenalGuard expands market for complex procedures, such as TAVR:

- **Surgery**: Improve Outcomes relative to Surgery
- **TAVR**: Increase Referrals
- **Very High-Risk Patients Otherwise Inoperable**: Candidates for Valve Replacement

Lowest Risk  Candidates for Valve Replacement  Highest Risk
- CIN remains a real and growing problem in modern cath lab

- Evidence continues to mount that RenalGuard can reduce the incidence of CIN and the adverse events associated with the condition

- Preventing CIN improves patient outcomes, reduces cath lab costs, improves hospital quality metrics, and can increase catheterization lab utilization and revenue.
Expanded Clinical Results
MYTHOS Trial: RenalGuard vs. Overnight Hydration

Rate of CI-AKI, n=170, randomized

- All Patients: 18% (18% reduction) vs. 4.6% (P=0.005)
- Emergency (NSTEMI): 32% (84% reduction) vs. 5% (P=0.003)
- Planned Procedures: 10% (60% reduction) vs. 4% (P=0.44)

n=292 at-risk patients, 4 sites, randomized

**SCr rise > 0.5 mg/dL**
- Sodium Bicarbonate: 6%
- RenalGuard: 15%
- P=0.003

**SCr rise > 25%**
- Sodium Bicarbonate: 2.7%
- RenalGuard: 13%
- P=0.001

**Dialysis**
- Sodium Bicarbonate: 4.8%
- RenalGuard: 0.7%
- P=0.031

Briguori. REMEDIAL II Circulation 2011.
AKIGUARD: Long-Term Outcomes

n=133, randomized

- CI-AKI: 25% (7% with RenalGuard, P=0.01)
- MACCE in 12 months: 32% (7% with RenalGuard, P<0.01)
- eGFR decrease in 3 months: 15% (0% with RenalGuard, P<0.01)

Hospital days in 12 months:
- Overnight Hydration: 4.9 (1.0 with RenalGuard, P=0.01)
- RenalGuard: -80%

TAVI new, growing (25% / year) procedure to replace aortic valves via catheter in patients too frail for surgery

- Up to 1/3 of TAVI patients develop CI-AKI
- CI-AKI strong predictor of 1-year mortality (47.9% vs. 15.7%)

n=112, randomized

P=0.014

No CI-AKI in patients without pre-existing kidney dysfunction
Clinical Studies

CI-AKI & TAVI

- n=48, not randomized
- Sodium Bicarbonate/NAC
- RenalGuard
- Significant reduction in incidence of CI-AKI
- Severe CI-AKI, strongest predictor of 1-year mortality, eliminated

High-risk patients received RenalGuard and were compared to lower-risk patients, who received control.