MANAGEMENT OF VOLUME OVERLOAD IN ADHF: THE GUIDELINES AND THE ART

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• **Employment:** Advocate Heart Institute

• **Consultation:** St. Jude, Medtronic, Respircardia, Axon Technologies

• **Research Grants to the Advocate Heart Institute:** Cardiokinetix, Impulse Dynamics, St. Jude, Novartis

• **Speaker Bureaus:** None

• **Stock Ownership:** None
**Congestion after Initial In-Hospital Therapy is Associated with Higher 60-day Mortality**

### 60-Day All-cause Mortality

<table>
<thead>
<tr>
<th>Condition</th>
<th>Overall</th>
<th>Na&lt;136</th>
<th>Na≥136</th>
<th>BUN&gt;29</th>
<th>BUN≤29</th>
</tr>
</thead>
<tbody>
<tr>
<td>N =</td>
<td>319</td>
<td>69</td>
<td>250</td>
<td>140</td>
<td>179</td>
</tr>
<tr>
<td>%</td>
<td></td>
<td>(21.6%)</td>
<td>(78.4%)</td>
<td>(44%)</td>
<td>(56%)</td>
</tr>
<tr>
<td>60-Day Mortality</td>
<td>6.3</td>
<td>14.5</td>
<td>4</td>
<td>11.4</td>
<td>2.2</td>
</tr>
<tr>
<td>0%</td>
<td>20%</td>
<td>10%</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
</tr>
</tbody>
</table>

* Edema, Dyspnea, and JVD at baseline

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Gheorghiade M et al. JAMA. 2004; 291: 1963
Survival after HF Hospitalizations

Median Survival (Years)

Setoguchi S et al. AHJ 2007; 154: 260-6
Diuretic Strategies in Patients with Acute Decompensated Heart Failure (DOSE) Trial: Primary End-Point

Patients’ Global Assessment of Symptoms during the 72-Hour Study-Treatment Period.
Secondary End Points for Each Treatment Comparison.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Bolus Every 12 Hr (N=156)</th>
<th>Continuous Infusion (N=152)</th>
<th>P Value</th>
<th>Low Dose (N=151)</th>
<th>High Dose (N=157)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC for dyspnea at 72 hr</td>
<td>4456±1468</td>
<td>4699±1573</td>
<td>0.36</td>
<td>4478±1550</td>
<td>4668±1496</td>
<td>0.04</td>
</tr>
<tr>
<td>Freedom from congestion at 72 hr — no./total no. (%)</td>
<td>22/153 (14)</td>
<td>22/144 (15)</td>
<td>0.78</td>
<td>16/143 (11)</td>
<td>28/154 (18)</td>
<td>0.09</td>
</tr>
<tr>
<td>Change in weight at 72 hr — lb</td>
<td>−6.8±7.8</td>
<td>−8.1±10.3</td>
<td>0.20</td>
<td>−6.1±9.5</td>
<td>−8.7±8.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Net fluid loss at 72 hr — ml</td>
<td>4237±3208</td>
<td>4249±3104</td>
<td>0.89</td>
<td>3575±2635</td>
<td>4899±3479</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in NT-proBNP at 72 hr — pg/ml</td>
<td>−1316±4364</td>
<td>−1773±3828</td>
<td>0.44</td>
<td>−1194±4094</td>
<td>−1882±4105</td>
<td>0.06</td>
</tr>
<tr>
<td>Worsening or persistent heart failure — no./total no. (%)</td>
<td>38/154 (25)</td>
<td>34/145 (23)</td>
<td>0.78</td>
<td>38/145 (26)</td>
<td>34/154 (22)</td>
<td>0.40</td>
</tr>
<tr>
<td>Treatment failure — no./total no. (%)†</td>
<td>59/155 (38)</td>
<td>57/147 (39)</td>
<td>0.88</td>
<td>54/147 (37)</td>
<td>62/155 (40)</td>
<td>0.56</td>
</tr>
<tr>
<td>Increase in creatinine of &gt;0.3 mg/dl within 72 hr — no./total no. (%)</td>
<td>27/155 (17)</td>
<td>28/146 (19)</td>
<td>0.64</td>
<td>20/147 (14)</td>
<td>35/154 (23)</td>
<td>0.04</td>
</tr>
<tr>
<td>Length of stay in hospital — days</td>
<td></td>
<td></td>
<td>0.97</td>
<td>6</td>
<td>5</td>
<td>0.55</td>
</tr>
<tr>
<td>Median</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>3–9</td>
<td>3–8</td>
<td>4–9</td>
<td>3–8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive and out of hospital — days</td>
<td></td>
<td></td>
<td>0.36</td>
<td>50</td>
<td>52</td>
<td>0.42</td>
</tr>
<tr>
<td>Median</td>
<td>51</td>
<td>51</td>
<td>50</td>
<td>52</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. To convert pounds to kilograms, divide by 2.2. AUC denotes area under the curve, and NT-proBNP N-terminal pro-brain natriuretic peptide.
† Treatment failure was defined as the development of any one of the following during the 72 hours after randomization: increase in serum creatinine level of more than 0.3 mg per deciliter (26.5 μmol per liter), worsening or persistent heart failure, clinical evidence of excessive diuresis requiring intervention (e.g., administration of intravenous fluids), or death.
Diuretic Strategies in Patients with Acute Decompensated Heart Failure: DOSE Trial: 60-Day Outcomes

Kaplan–Meier Curves for the Clinical Composite End Point of Death, Rehospitalization, or Emergency Department Visit.

A Bolus vs. Continuous Infusion

Hazard ratio with continuous infusion, 1.15 (95% CI, 0.83–1.60)
P = 0.41

B Low-Dose vs. High-Dose Strategy

Hazard ratio with high-dose strategy, 0.83 (95% CI, 0.60–1.16)
P = 0.28

# Pharmacological Therapy: Diuretics

<table>
<thead>
<tr>
<th>Diuretics</th>
<th>Strength</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous loop diuretics are recommended for all patients with AHF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of i.v. diuretics.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>In patients with new-onset AHF or those with chronic, decompensated HF not receiving oral diuretics the initial recommended dose should be 20–40 mg i.v. furosemide (or equivalent); for those on chronic diuretic therapy, initial i.v. dose should be at least equivalent to oral dose.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>It is recommended to give diuretics either as intermittent boluses or as a continuous infusion, and the dose and duration should be adjusted according to patients’ symptoms and clinical status.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Combination of loop diuretic with either thiazide-type diuretic or spironolactone may be considered in patients with resistant oedema or insufficient symptomatic response.</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

2013 AHA/ACC Guidelines for the Treatment of HF in the adult
Mechanisms of Loop Diuretic Resistance

Pathophysiology
- Failing heart
  - ↓ CO
  - ↓ Plasma albumin
- Intestines
  - ↑ CVP
  - Unable to bind to albumin
- Bowman’s capsule
  - ↓ RBF and GFR
  - ↑ RAAS and SNS
  - Reduced filtration
  - Proximal Na reabsorption
  - Organic acids like blood urea nitrogen competitively bind to OAT, reducing diuretic availability in the tubule
  - Filtered albumin binds to furosemide, reducing availability at cotransporter
- Na–K–Cl cotransporter
  - Braking phenomenon
    - ↑ RAAS and SNS
  - Distal Na reabsorption
- Urine

Definitions of Diuretic Resistance and Measures of Diuretic Response

**Box 1 | Definitions of diuretic resistance**
- Persistent congestion despite adequate and escalating doses of diuretic with >80 mg furosemide per day\(^{107}\)
- Amount of sodium excreted as a percentage of filtered load <0.2\(^{108}\)
- Failure to excrete at least 90 mmol of sodium within 72 h of a 160 mg oral furosemide dose given twice daily\(^{109}\)

**Box 2 | Metrics of diuretic response**
- Weight loss per unit of 40 mg furosemide (or equivalent)\(^5,^{51}\)
- Net fluid loss per milligram of loop diuretic (40 mg of furosemide or equivalent) during hospitalization\(^6\)
- Natriuretic response to furosemide as the ratio of urinary sodium to urinary furosemide\(^52\)

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ter Maaten, J. M. *et al.* Nat. Rev. Cardiol. 12, 184–192 (2015);
Why Ultrafiltration in Heart Failure?

Chronic heart failure

RAAS Activation
SNS Activation
Renal Hypoperfusion
Non-osmotic AVP release

Decreased cardiac output

Hemodynamically driven reduction in GFR ("Pre-renal")
- NGAL, Cystatin-C, KIM-1

Ischemic renal tubular injury
+ NGAL, + Cystatin-C, + KIM-1

Decrease Water Clearance
+ Increased Sodium Reabsorption

Diuretics

Hypotonic Urine

Diuretic Resistance
- Braking phenomenon, DT adaptation, Uremic Anions, Proteinuria

Volume Overload

Advantages of Ultrafiltration

- Predictable removal of sodium and fluids
- No direct neurohormonal activation
- No changes in electrolytes, particularly K and Mg

Ultrafiltration

Water flux contains sodium (nearly isotonic to plasma water)

1/1 of ultrafiltrate contains 1/3 of renal sodium, equivalent to 5 g of salt

Sodium removed from patient, no concentration changes
## Comparative Characteristics of Loop Diuretics and Isolated Ultrafiltration

<table>
<thead>
<tr>
<th>Loop Diuretics</th>
<th>Isolated Ultrafiltration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct neurohormonal activation</td>
<td>No direct neurohormonal activation</td>
</tr>
<tr>
<td>Elimination of hypotonic urine</td>
<td>Removal of isotonic plasma water</td>
</tr>
<tr>
<td>Unpredictable elimination of sodium and water</td>
<td>Precise control of rate and amount of fluid removal</td>
</tr>
<tr>
<td>Development of diuretic resistance with prolonged administration</td>
<td>Restoration of diuretic responsiveness</td>
</tr>
<tr>
<td>Risk of hypokalemia and hypomagnesemia</td>
<td>No effect on plasma concentration of potassium and magnesium</td>
</tr>
<tr>
<td>Peripheral venous access</td>
<td>Peripheral or central venous catheter</td>
</tr>
<tr>
<td>No need for anticoagulation</td>
<td>Need for anticoagulation</td>
</tr>
<tr>
<td>No extracorporeal circuit</td>
<td>Need for extracorporeal circuit</td>
</tr>
</tbody>
</table>

Costanzo MR et al. JACC 2017, in press
Two Contemporary Ultrafiltration Devices
CARRESS:
Treatment Prescriptions in the Two Arms of the Study

**Stepped Pharmacologic Therapy**

<table>
<thead>
<tr>
<th>Current Dose</th>
<th>Suggested Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>≤ 80 loor (day)</td>
<td>+ or -</td>
</tr>
<tr>
<td>81-160</td>
<td>+ or - 40 mg iv bolus + 10 mg/hr</td>
</tr>
<tr>
<td>161-240</td>
<td>+ or - 40 mg iv bolus + 20 mg/hr</td>
</tr>
<tr>
<td>&gt; 240</td>
<td>+ or - 40 mg iv bolus + 30 mg/hr</td>
</tr>
</tbody>
</table>

**Ultrafiltration**

Persistent Volume Overload
- If blood pressure stable and no evidence of significant intravascular volume depletion → Continue ultrafiltration at same rate of fluid removal – 200cc/hour
- If blood pressure drops significantly or there is evidence of significant intravascular volume depletion → decrease rate of ultrafiltration to 100cc/hour or discontinue – resume ultrafiltration when the clinical picture has stabilized

**AT 24 Hrs - STEPPED PHARMACOLOGIC CARE ARM**
Persistent Volume Overload Present
- UO > 5 L/day → Reduce current diuretic regimen if desired
- UO 3-5 L/day → Continue current diuretic regimen
- UO < 3 L/day → Advance to next step on table

**AT 48 Hrs - STEPPED PHARMACOLOGIC CARE ARM**
Persistent Volume Overload Present
- UO > 5 L/day → Reduce current diuretic regimen if desired
- UO 3-5 L/day → Continue current diuretic regimen
- UO < 3 L/day → Advance to next step on table and consider:
  - Dopamine or dobutamine at 2 ug/kg/hr if SBP < 110 mmHg and EF < 40% or RV systolic dysfunction
  - Nitroglycerin or Nesiritide if SBP > 120 (any EF) and Severe Symptoms
CARRESS
Changes in Serum Creatinine and Weight at 96 Hours (Bivariate Response)

WRF and IRF were defined by:

A: >0.3 mg/dL change in serum Creatinine
B: ≥20% change in eGFR

Among patients hospitalized with HF, transient increases in creatinine cannot be equated to renal preservation, and do not necessarily reflect renal injury or adverse long-term prognosis.

The rate of fluid removal was mandated to be the same (200 ml/h) in ALL patients assigned to UF.

No information on the incidence and severity of RV dysfunction in the patient population.

- Patients with RV dysfunction are especially susceptible to the development of hypovolemia from fluid removal because of the greater blood volume stored in the venous circulation.

Patients assigned to UF were not allowed to receive any vasoactive drugs, including vasodilators and inotropic drugs.

12% of the medical therapy arm received IV inotropes, which may have prevented or attenuated worsening renal function resulting from a lower blood pressure.
The average ultrafiltration treatment duration was approximately **48 hours** whereas the average medical treatment lasted up to **96 hours** for the same amount of fluid removal.

While the same fluid removal rate was used in the UF group, diuretic therapy itself could be adjusted in the medical treatment group and, in fact, nearly 50% of the patients in this group received both loop and thiazide diuretics

**20 % cross-over rate!**

8/94 patients (**9%**) in the UF group NEVER received UF!

28/94 patients (**30%**) in the UF group received IV diuretics before the 96-hour assessment!

No information on wether the magnitude of CKD was comparable in the 2 groups. Severity and duration of underlying CKD are key risk factors for AKI
Aquapheresis Versus Intravenous Diuretics and Hospitalizations for Heart Failure

Maria Rosa Costanzo, MD, Daniel Negoianu, MD, Brian E. Jaski, MD, Bradley A. Bart, MD, James T. Heywood, MD, Inder S. Anand, MD, DPHIL (OXON), James M. Smelser, MD, Alan M. Kaneshige, MD, Don B. Chomsky, MD, Eric D. Adler, MD, Garrie J. Haas, MD, James A. Watts, MD, Jose L. Nabut, MS, Michael P. Schollmeyer, DVM, Gregg C. Fonarow, MD

Study Design and Objective

- Prospective, one-to-one randomized, non-blinded multicenter trial (NCT01474200)
- To determine whether early isolated Veno-Venous Ultrafiltration prolongs time to first HF event within 90 days after discharge from the index HF hospitalization compared to IV Loop Diuretics when both fluid removal therapies are adjusted according to the patients’ vital signs and renal function.

Costanzo MR, Negoianu D, Fonarow GC et al. Rationale and design of the Aquapheresis Versus Intravenous Diuretics and Hospitalization for Heart Failure (AVOID-HF) trial. Am Heart J 2015; http://dx.doi.org/10.1016/j.ahj.2015.05.019
The original sample size of 810 patients was based on the assumption that combined 90 day event rate would be 25% for the ALD group, and that the treatment effect of AUF would be a 35%-37.5% reduction in 90 day HF events, or a Hazard Ratio (HR) = 0.616 - 0.590 (90% power).

The AVOID-HF trial was supported by Gambro (Lund, SW) from its inception in March 2012 until the acquisition of the Sponsor by Baxter Healthcare (Deerfield, IL. U.S.A.) in September 2013.

In April 2014 the Sponsor stopped the study prematurely because of slower-than-projected study enrollment.

This decision was made without advance review of the trial data and without prior consultation with the study’s DSMB or the Steering Committee, which disagreed with the Sponsor's decision to stop the trial.

Trial’s termination was in no way related to futility or safety concerns.

A total of 224 patients (mean number of 6.5 patients per site) had been enrolled in the AVOID-HF trial at the time of its termination.
Primary Endpoint

- Time to first heart failure event within 90 days after discharge from index hospitalization

- Heart Failure Events are defined as:
  - Heart Failure Rehospitalization or
  - Unscheduled clinic or emergency room visits in which the patient receives either IV loop diuretics or ultrafiltration for fluid overload due to heart failure

Costanzo MR, Negoianu D, Fonarow GC et al. Rationale and design of the Aquapheresis Versus Intravenous Diuretics and Hospitalization for Heart Failure (AVOID-HF) trial. Am Heart J 2015; http://dx.doi.org/10.1016/j.ahj.2015.05.019
Inclusion Criteria

- 18 years or older
- Male or non-pregnant females
- On daily oral diuretics
- Admitted to hospital with the primary diagnosis of acutely decompensated HF
- Fluid Overload manifested by at least two of the following:
  - ≥ 2+ pitting edema
  - Jugular venous distension > 8 cm
  - Pulmonary edema or Pleural effusion on x-ray
  - Paroxysmal nocturnal dyspnea or ≥ two-pillow orthopnea
  - Respiratory rate ≥ 20 /minute
- Must be enrolled in trial ≤ 24 hrs of hospital admission
- Received ≤ 2 doses IV loop diuretics before randomization
- Provide Informed Consent

Costanzo MR, Negoianu D, Fonarow GC et al. Rationale and design of the Aquapheresis Versus Intravenous Diuretics and Hospitalization for Heart Failure (AVOID-HF) trial. Am Heart J 2015; http://dx.doi.org/10.1016/j.ahj.2015.05.019
Costanzo MR, Negoianu D, Fonarow GC et al. Rationale and design of the Aquapheresis Versus Intravenous Diuretics and Hospitalization for Heart Failure (AVOID-HF) trial. Am Heart J 2015; 170:471–482
Costanzo MR, Negoianu D, Fonarow GC et al. Rationale and design of the Aquapheresis Versus Intravenous Diuretics and Hospitalization for Heart Failure (AVOID-HF) trial. Am Heart J 2015; 170:471–482
ADJUSTABLE DIURETICS

Consider Completion of Therapy if ONE of the following:

- Resolution of congestion (all of the following):
  - JVP < 8 cm H2O
  - No orthopnea
  - Trace or no peripheral edema

- Best achievable “dry weight” has been achieved

  - Hemodynamic evidence of poor tolerance of fluid removal by persistent hemodynamic changes
  - AND
  - Net negative < 1 liter/24 hours

- Persistent elevation in sCr > 1.0 mg/dl above baseline at start of IV Diuretic Treatment

- Persistent hemodynamic instability

ADJUSTABLE UF

After completion of UF therapy

- If satisfactory “dry weight” has been reached AND sCr is stable:
  - Initiate oral loop diuretic therapy with goal to keep net even
  - GOMT

- If sCr, hemodynamics or UO are NOT stable:
  - Hold diuretics until creatinine is stable for a minimum of 12 hours and then:
  - If “dry weight”/adequate decongestion has been reached then initiate oral diuretics with goal to keep net even
  - If “dry weight”/adequate decongestion has NOT been reached then initiate IV diuretics

  - If elevated sCr or hemodynamic instability present, then consider a bolus of IV fluid

Costanzo MR, Negoianu D, Fonarow GC et al. Rationale and design of the Aquapheresis Versus Intravenous Diuretics and Hospitalization for Heart Failure (AVOID-HF) trial. Am Heart J 2015; 170:471–482
Primary End-Point:
Time to HF Event After Discharge

### Secondary Endpoints: Clinical

<table>
<thead>
<tr>
<th>Endpoint at 30 Days after Discharge/days at risk*</th>
<th>AUF N=105</th>
<th>ALD N=108</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of HF re-hospitalizations</td>
<td>11/2,876</td>
<td>24/2,882</td>
<td>0.060</td>
</tr>
<tr>
<td>Number of ED/unscheduled office visits</td>
<td>4/2,869</td>
<td>5/2,863</td>
<td>0.737</td>
</tr>
<tr>
<td>Number of patients with HF re-hospitalization</td>
<td>10 (9.5%)</td>
<td>22 (20.4%)</td>
<td>0.034</td>
</tr>
<tr>
<td>Number of days re-hospitalized for HF</td>
<td>68/2,933</td>
<td>172/3,030</td>
<td>0.029</td>
</tr>
<tr>
<td>Number of CV re-hospitalizations</td>
<td>17/2,882</td>
<td>33/2,891</td>
<td>0.037</td>
</tr>
<tr>
<td>Number of patients with CV re-hospitalization</td>
<td>15 (14.3%)</td>
<td>27 (25.0%)</td>
<td>0.042</td>
</tr>
<tr>
<td>Number of days for CV re-hospitalization</td>
<td>88/2,953</td>
<td>207/3,065</td>
<td>0.018</td>
</tr>
<tr>
<td>All-cause re-hospitalization rates</td>
<td>26/2,891</td>
<td>37/2,895</td>
<td>0.237</td>
</tr>
<tr>
<td>Days alive and out of hospital</td>
<td>27.3(5.8)</td>
<td>26.5(6.3)</td>
<td>0.333</td>
</tr>
</tbody>
</table>

*No statistically significant differences between groups were observed in these variables at 90 days*
<table>
<thead>
<tr>
<th>Time Point</th>
<th>AUF (N=110) Mean ± SD</th>
<th>ALD (N=111) Mean ± SD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hours</td>
<td>0.02 ± 0.24</td>
<td>0.03 ± 0.24</td>
<td>0.692</td>
</tr>
<tr>
<td>48 hours</td>
<td>0.13 ± 0.88</td>
<td>0.05 ± 0.30</td>
<td>0.565</td>
</tr>
<tr>
<td>72 hours</td>
<td>0.09 ± 0.38</td>
<td>0.05 ± 0.35</td>
<td>0.875</td>
</tr>
<tr>
<td>96 hours</td>
<td>0.02 ± 0.30</td>
<td>0.07 ± 0.45</td>
<td>0.579</td>
</tr>
<tr>
<td>120 hours</td>
<td>-0.05 ± 0.23</td>
<td>0.06 ± 0.49</td>
<td>0.289</td>
</tr>
<tr>
<td>Discharge</td>
<td>0.12 ± 0.42</td>
<td>0.12 ± 0.50</td>
<td>0.527</td>
</tr>
<tr>
<td>30 days</td>
<td>0.37 ± 3.41</td>
<td>0.17 ± 0.63</td>
<td>0.450</td>
</tr>
<tr>
<td>60 days</td>
<td>0.09 ± 0.52</td>
<td>-0.01 ± 0.44</td>
<td>0.115</td>
</tr>
<tr>
<td>90 days</td>
<td>-0.30 ± 0.42</td>
<td>-0.26 ± 0.30</td>
<td>0.829</td>
</tr>
</tbody>
</table>

Changes in Serum Creatinine (mg/dL) up to 90 Days after Randomization
**Mechanistic Studies:**

- Evaluation of diuretic responsiveness at baseline, during and after fluid removal.

- Measurement of hemodynamic values reflecting fluid status at baseline and throughout therapy.

- Establishment of specific hemodynamic targets indicative of euvolemia.

- Comparison of different UF rates in terms of their ability to achieve these targets without causing actual renal tubular damage.

- Simultaneous measurement of the selected hemodynamic values and biomarkers levels that can differentiate rises in sCr due to decreases in GFR due to fluid removal from those reflective of actual renal injury.

- The results of these mechanistic studies are essential to the performance of “precision” fluid removal in future controlled trials.
Development of vascular accesses and UF device components that increase the efficiency and safety of the therapy.

Evaluation of device- and therapy-related AEs to determine which are preventable or related to operator experience versus those inherent to the manner of therapy delivery, or unpredictable.

Design of an adequately powered study to prospectively compare UF with pharmacological fluid removal therapies.
- All treatments tailored to individual patients’ hemodynamic and renal status
- Follow up period sufficiently long to permit evaluation of the effects of fluid removal on both morbidity (re-hospitalizations) and mortality.
- Evaluation of whether the greater cost of mechanical fluid removal during the index hospitalization is offset by the cost savings resulting from fewer HF events in UF-treated patients.

Outpatient studies to determine the relative safety and effectiveness of intermittent pharmacological and mechanical fluid removal therapies for prevention, rather than treatment of HF decompensation.

Studies of intermittent outpatient UF to restore responsiveness to oral diuretics

Development of ‘wearable” UF devices delivering individualized UF therapy to fluid overloaded HF patients.
New Gentle UF concept: gentle ultrafiltration complementary to low-dose IV diuretics with peripheral single needle access

Patient cohort in Pure HF: Symptomatic HF patients admitted to the hospital due to congestion, not fully responsive to diuretic therapy.

⇒ 864 patients in 30 centers in 7 countries

**Ultrafiltration group**

Peripheral UF

+ Low-dose IV diuretics

- 1-7 UF sessions
- (6-10h/ day-time session, 1-10 days)

**Control group**

Guideline-directed medical therapy incl. IV diuretics

Follow-up: 30- and 90-days

Primary endpoint:

→ Heart failure event in 90 days after discharge

→ Cardiovascular death in 90 days after randomization

HF event: a HF rehospitalization OR unscheduled outpatient visit OR emergency room treatment with IV diuretics or UF