Place of Isolated Ultrafiltration in Management of Congestive Heart Failure

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& Medical Board FMC, Bad Homburg, G

lundi 28 et mardi 29 avril 2014
Speaker name: Prof. Bernard Canaud

- [ ] I have the following potential conflicts of interest to report:
  - [ ] Consulting
  - [x] Employment in industry (FMC)
  - [ ] Shareholder in a healthcare company
  - [ ] Owner of a healthcare company
  - [ ] Other(s)
  - [ ] I do not have any potential conflict of interest
Outlook of the Presentation

- Heart failure and cardiorenal syndrome
- Management of congestive heart failure
- Indication of ultrafiltration in CRS
- Role of ultrafiltration in CRS
  - Observational clinical reports of ultrafiltration in CRS
  - Interventional clinical trials of ultrafiltration in CRS
- Remaining questions
- Take home message
# Incidence and prevalence of Heart Failure in USA

## AHA Statistical Update

### Heart Disease and Stroke Statistics—2010 Update

A Report From the American Heart Association

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Both sexes</td>
<td>5 800 000 (2.6%)</td>
<td>670 000</td>
<td>282 754</td>
<td>1 106 000</td>
<td>$39.2 billion</td>
</tr>
<tr>
<td>Males</td>
<td>3 100 000 (3.1%)</td>
<td>350 000</td>
<td>123 600 (43.7%)†</td>
<td>523 000</td>
<td>...</td>
</tr>
<tr>
<td>Females</td>
<td>2 700 000 (2.1%)</td>
<td>320 000</td>
<td>159 167 (56.3%)†</td>
<td>583 000</td>
<td>...</td>
</tr>
</tbody>
</table>

*Annual Crude Mortality 4.9%*  

ADHERE : Acute Decompensated Heart Failure National Registry

Lloyd-Jones et al. Circulation 2010; 121:e46-e215
## Classification of Heart Failure

### New York Heart Association (NYHA) Dyspnea Staging System

<table>
<thead>
<tr>
<th>Class</th>
<th>Patient symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (Mild)</td>
<td>• No limitation of activity&lt;br&gt;• No symptoms with normal activity</td>
</tr>
<tr>
<td>Class II (Mild)</td>
<td>• Slight limitation of activity&lt;br&gt;• Comfortable with rest or mild exertion</td>
</tr>
<tr>
<td>Class III (Moderate)</td>
<td>• Marked limitation of activity&lt;br&gt;• Comfortable only at rest</td>
</tr>
<tr>
<td>Class IV (Severe)</td>
<td>• Complete rest is required; confined to bed or chair&lt;br&gt;• Any activity brings discomfort; symptoms occur at rest</td>
</tr>
</tbody>
</table>

### American College of Cardiology (ACC)/American Heart Association (AHA) Staging System 2001

<table>
<thead>
<tr>
<th>Class</th>
<th>Lesions and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage A</td>
<td>• No structural abnormality of the heart&lt;br&gt;• No symptoms of HF</td>
</tr>
<tr>
<td>Stage B</td>
<td>• Structural abnormality of the heart&lt;br&gt;• No symptoms of HF</td>
</tr>
<tr>
<td>Stage C</td>
<td>• Structural abnormality of the heart&lt;br&gt;• Some symptoms of HF</td>
</tr>
<tr>
<td>Stage D</td>
<td>• Structural abnormality of the heart&lt;br&gt;• Symptoms of HF that do not respond well to normal treatment</td>
</tr>
</tbody>
</table>

Hunt S et al. *J Am Coll Cardiol* 2009;53:e1–e90
<table>
<thead>
<tr>
<th>CRS Type I (Acute Cardiorenal Syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abrupt worsening of cardiac function leading to acute kidney injury</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CRS Type II (Chronic Cardiorenal Syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) causing progressive and permanent chronic kidney disease</strong></td>
</tr>
</tbody>
</table>
A Common Feature to CRS I and II

CRS Type I (Acute Cardiorenal Syndrome)
Abrupt worsening of cardiac function leading to acute kidney injury

CRS Type II (Chronic Cardiorenal Syndrome)
Chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) causing progressive and permanent chronic kidney disease

Salt and Water Retention

Congestion

CardioRenal Syndrome: Expression of Mutual Dysfunction

A pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ.
Cardiorenal Vicious Circle

Congestion Results from Neurohumoral Adaptation

↑ Adrenergic System
↑ Norepinephrine
↑ Vasopressin, AVP

Endothelial Dysfunction
↑ Endothelin1, ↑ NO

↑ Renin
Angiotensin II
↑ Aldosterone

↑ Cardiac Output
↓ BNP

Hypotension

Effective Hypovolemia

Cardiovascular Failure

Edema Congestion

Neurohumoral Adaptation

Renal Injury

Angiotensin II

Congestion Results

Aldosterone
Congestion Results From the Imbalance of Neurohumoral Mediators

Vasoconstriction
Salt & Water Retention

Vasodilation
Salt & Water Excretion

Norepinephrine
Epinephrine
Renin
Angiotensin II
Aldosterone
Vasopressin
Endothelin I
ATP, Adenosine…

Prostaglandin
(PGE2, PGI)
Natriuretic Peptides
(ANP, BNP)
NO, Dopamine
…
Stepwise Approach for Managing Heart Failure in Adults - 2003

Stage A: High risk with no symptoms
- Risk-factor reduction, patient and family education
- ACE inhibitors or ARBs in some patients
- Treat hypertension, diabetes, dyslipidemia; ACE inhibitors or ARBs in some patients

Stage B: Structural heart disease, no symptoms
- ACE inhibitors and beta-blockers in all patients
- Dietary sodium restriction, diuretics, and digoxin
- Cardiac resynchronization if bundle-branch block present
- Consider multidisciplinary team
- Revascularization, mitral-valve surgery

Stage C: Structural disease, previous or current symptoms
- ACE inhibitors or ARBs in all patients; beta-blockers in selected patients
- Risk-factor reduction, patient and family education

Stage D: Refractory symptoms requiring special intervention
- Inotropes
- VAD, transplantation
- Aldosterone antagonist, nesiritide
- Hospice

Stage D Heart Failure: End Stage?
Stage D Heart Failure: What to Propose?

- **Palliative**
  - Nursing
  - Psychological, Antalgic...

- **Curative**
  - Heart transplant
  - Regenerative medicine

- **Supportive**
  - Heart Assistance
  - **Ultrafiltration**
  - Anemia & Iron therapies
Cardiorenal Syndrome: A Complete Picture

CRAS, Cardio Renal Anemic Syndrome
CRIDS, Cardio Renal Inflammatory Deficiency Syndrome
CRAIDS, Cardio Renal Anemic Inflammatory Iron Deficiency Syndrome

Macdougall IC et al, Europ J Heart Fail. 2012; 14:882-886
A Mechanistic Approach to Treat CardioRenal Syndrome and Congestion: Mechanical Natriuresis

Breaking Cardiorenal Vicious Circle

- Hypovolemia
- Hypotension
- Increased Adrenergic System
- Increased BNP
- Decreased Cardiac Output

Effective Hypovolemia

- Increased Norepinephrine
- Increased Vasopressin, AVP
- Increased Renin
- Increased Angiotensin II
- Increased Aldosterone
- Endothelial Dysfunction
  - Increased Endothelin1, NO

Edema Congestion
- Isolated Ultrafiltration
- Na & Water Depletion

Na & Water Depletion

Cardiorenal Syndrome (CHF)

Renal Failure (AKI)
Treatment of Severe Fluid Overload by Ultrafiltration

Isolated Ultrafiltration with pediatric kit on SCUF-Multifiltrate®
What is Isolated Ultrafiltration?
= Mechanical Natriuresis

<table>
<thead>
<tr>
<th>Urine + Furosemide</th>
<th>Ultrafiltrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mmol/l</td>
<td>150 mmol/l</td>
</tr>
<tr>
<td>6 g NaCl</td>
<td>9 g NaCl</td>
</tr>
</tbody>
</table>

Per liter removed
What is Different With Isolated Ultrafiltration?

**Metabolic**
- Isoosmotic removal
  - No body osmotic change
  - Cl removal (Gibbs-Donnan semi-permeable membrane)
- No significant clearing effects
  - Urea...
  - Potassium
  - Bicarbonate
  - Ca, Mg....
- Hemoconcentration
  - Total Protein, Hematocrit increase
- Removal of inflammatory mediators?

**Hemodynamic**
- Facilitate refilling rate and balance ultrafiltration rate
- Preserve volemia
- Ensure negative thermal balance
- Ensure PVC and positive inotropic action

Cardiac Output
Vascular Refilling
Peripheral Vasc. Resistance
A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the International Society for Heart and Lung Transplantation
Class IIa

1. When patients present with acute HF and known or suspected acute myocardial ischemia due to occlusive coronary disease, especially when there are signs and symptoms of inadequate systemic perfusion, urgent cardiac catheterization and revascularization is reasonable where it is likely to prolong meaningful survival. *(Level of Evidence: C)*

...  

4. Ultrafiltration is reasonable for patients with refractory congestion not responding to medical therapy. *(Level of Evidence: B)*
ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: John J.V. McMurray (Chairperson) (UK)*, Stamatis Adamopoulos (Greece), Stefan D. Anker (Germany), Angelo Auricchio (Switzerland), Michael Böhm (Germany), Kenneth Dickstein (Norway), Volkmar Falk (Switzerland), Gerasimos Filippatos (Greece), Cândida Fonseca (Portugal), Miguel Angel Gomez-Sanchez (Spain), Tiny Jaarsma (Sweden), Lars Køber (Denmark), Gregory Y.H. Lip (UK), Aldo Pietro Maggioni (Italy), Alexander Parkhomenko (Ukraine), Burkert M. Pieske (Austria), Bogdan A. Popescu (Romania), Per K. Rønnevik (Norway), Frans H. Rutten (The Netherlands), Juerg Schwitter (Switzerland), Petar Seferovic (Serbia), Janina Stepinska (Poland), Pedro T. Trindade (Switzerland), Adriaan A. Voors (The Netherlands), Faiez Zannad (France), Andreas Zeiher (Germany).
Practical Guideline For Managing Heart Failure

Acute pulmonary oedema/congestion

- Hypoxaemia
  - Yes: Oxygen therapy
  - No: Consider vasodilators
- Severe anxiety/distress
  - Yes: Consider lignocaine
  - No: Measure central venous blood pressure
- Measure central venous blood pressure
  - SBP <85 mmHg or shock: Add non-vasodilating therapy
  - SBP 85–110 mmHg: No additional therapy until response assessed
  - SBP >110 mmHg: Consider vasodilator (e.g. NTG)
- Adequate response to treatment
  - Yes: Continue present treatment
  - No: Re-evaluation of patient’s clinical status

SBP <85 mmHg:
- Yes: Stop vasodilator
- No: Re-evaluation of patient’s clinical status

SpO₂ <90%:
- Yes: Consider endotracheal intubation
- No: Consider right-ventricular catheterization

Urine output <20 mL/h:
- Yes: Bladder catheterization to confirm
- No: Consider low-dose dopamine

Refractory
- Yes: Bladder catheterization to confirm
- No: Consider right-heart catheterization

Reference:
European Heart Journal 2012; 33, 1787–1847
12.2.2.3 Ultrafiltration

Venovenous isolated ultrafiltration is sometimes used to remove fluid in patients with HF,\textsuperscript{232} although is usually reserved for those unresponsive or resistant to diuretics.
## Clinical Reports Assessing UF in CHF

<table>
<thead>
<tr>
<th>Study, Author</th>
<th>Study type and Design</th>
<th>N Pats</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUPHORIA, Costanzo, J Card Fail. 2004</td>
<td>Prospective, monocenter study, Early SCUF/IV diuretics</td>
<td>20</td>
<td>Safety and efficacy of SCUF&lt;br&gt;Clinical improvement</td>
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<td>Costanzo, J Card Fail. 2004</td>
<td>Prospective, cohort series, Early SCUF/IV diuretics</td>
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<td>Safety and efficacy of SCUF&lt;br&gt;Clinical improvement - Superiority of SCUF</td>
</tr>
<tr>
<td>Bart, J Card Fail. 2004</td>
<td>Randomized, monocenter study, Early SCUF/IV diuretics</td>
<td>20/20</td>
<td>Safety and efficacy of SCUF&lt;br&gt;Clinical improvement - Superiority of SCUF</td>
</tr>
<tr>
<td>Sheppard, J Card Fail. 2004</td>
<td>Retrospective, cohort series, NYHAIV - SCUF</td>
<td>19</td>
<td>Safety and efficacy of SCUF&lt;br&gt;Clinical improvement</td>
</tr>
<tr>
<td>Jaski, J Card Fail. 2003</td>
<td>Prospective, cohort series, NYHAIII SCUF, Long term follow up</td>
<td>21</td>
<td>Safety and efficacy of SCUF&lt;br&gt;Clinical improvement</td>
</tr>
<tr>
<td>Marenzi, J Am Coll Cardiol. 2001</td>
<td>Prospective, cohort series, NYHAIV</td>
<td>24</td>
<td>Safety and efficacy of SCUF&lt;br&gt;Clinical and hemodynamic improvement</td>
</tr>
<tr>
<td>Canaud, Am J Kid Dis. 1996</td>
<td>Retrospective, cohort series, NYHAIV - SCUF</td>
<td>52</td>
<td>Safety and efficacy of SCUF&lt;br&gt;Clinical improvement in responders 75%</td>
</tr>
<tr>
<td>Agostini, Am J Med. 1994</td>
<td>Randomized, monocenter SCUF/IV diuretics</td>
<td>8/8</td>
<td>Safety and efficacy of SCUF&lt;br&gt;Clinical improvement - Superiority and durability of SCUF</td>
</tr>
<tr>
<td>Pepi, Br Heart J. 1993</td>
<td>Randomized, monocenter, NYHAII/III - SCUF / conventional care</td>
<td>12/12</td>
<td>Safety and efficacy of SCUF&lt;br&gt;Clinical improvement - Superiority of SCUF</td>
</tr>
<tr>
<td>Agostini, J Am Coll Cardiol. 1993</td>
<td>Randomized, controlled, NYHAII-IV</td>
<td>18/18</td>
<td>Safety and efficacy of SCUF&lt;br&gt;Clinical improvement - Superiority of SCUF</td>
</tr>
<tr>
<td>Marenzi, Am J Med. 1993</td>
<td>Prospective, cohort series, NYHAII-IV</td>
<td>32</td>
<td>Safety and efficacy of SCUF&lt;br&gt;Clinical and hemodynamic improvement</td>
</tr>
</tbody>
</table>
Place of Ultrafiltration in the Clinical Setting

52 patients (M: 40, F: 12) - Age 63.8±10.2 y.o.
Congestive Heart Failure, NYHA IV – Stage D Refractory to Optimized Treatment

SCUF

Non-responders

UF Failure
13 patients

Death < 1 month

Responders

Partial recovery
15 patients

UF-HDF-PD
Heart + Kidney TPL 1

Total recovery
24 patients

Medications
Heart TPL 4

## Main Interventional Controlled Trials of UF in CHF

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Trial Design</th>
<th>Reference</th>
</tr>
</thead>
</table>
# Summary of Interventional Controlled Trials of UF in CHF

<table>
<thead>
<tr>
<th>Study</th>
<th>n Pt</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAFE</td>
<td>21</td>
<td>UF &gt;1l/8h  I ary UF3.6 ±1[6.4]L</td>
<td>Well tol. - No AE</td>
</tr>
<tr>
<td>RAPID-CHF</td>
<td>20/20</td>
<td>UF8hr/USC  I ary UF4.6L - WL24h sup. UF arm</td>
<td>Well tol. – No AE</td>
</tr>
<tr>
<td>EUPHORIA</td>
<td>7/13</td>
<td>UF8hr/USC  I ary UF6L - WL24h sup. UF arm</td>
<td>Well tol. – No AE</td>
</tr>
<tr>
<td>UNLOAD</td>
<td>100/100</td>
<td>UF24hr/USC  I ary UF: WL24h&gt; - Dysp↓-Creat↑  II ary 90dUF: Hosp↓ -Creat= -Mort. 9.6/11.6%</td>
<td>Well tol. – No AE</td>
</tr>
<tr>
<td>CARRESS-HF</td>
<td>94/94</td>
<td>UF72hr/SPI  I ary UF: WL72h = - Dysp = - Creat↑  II ary 90dUF: Hosp= - Creat = -Mort. 14/17%</td>
<td>SAE – Hemorrhage (cath, GI) – Sepsis (cath)</td>
</tr>
</tbody>
</table>

UF isolated ultrafiltration – USC usual standard care – SPI stepped pharmacological intervention
WL weight loss – d day – GI gastrointestinal – Well tol. Well tolerated – AE Adverse events SAE serious adverse events
Peripherally Inserted Venovenous Ultrafiltration

Methods: A simplified peripheral ultrafiltration system including a miniaturized disposable circuit was evaluated in patients with volume-overload states. Separate intravenous catheters (16–18 G) for withdrawal and return of blood (blood flow ≤ 40 mL/min, ultrafiltrate ≤ 500 mL/h) were placed by nonphysician personnel in upper extremity veins. Twenty-five treatments of up to 8 hours were performed in 21 patients.

Results: The primary endpoint of greater than 1 L fluid removal in less than 8 hours was achieved in 23 of 25 treatments. On average, 2611 ± 1002 mL (maximum 3,725 mL) of ultrafiltrate was removed per treatment (treatment period 6:43 ± 1:47 hours:minutes). Patient weight decreased from 91.9 ± 17.5 to 89.3 ± 17.3 kg (P < .0001) after ultrafiltration. No major adverse events occurred.
Peripherally Inserted Venovenous Ultrafiltration, PUF

## PUF Primary Endpoint:
**Clinical and Biochemical Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-UF</th>
<th>Discharge</th>
<th>30 Days</th>
<th>90 Days</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>87 ± 23</td>
<td>81 ± 22</td>
<td>84 ± 21</td>
<td>80 ± 18</td>
<td>.006</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>120 ± 17</td>
<td>114 ± 22</td>
<td>120 ± 26</td>
<td>116 ± 24</td>
<td>.306</td>
</tr>
<tr>
<td>Cr (mg/dL)</td>
<td>2.12 ± 0.6</td>
<td>2.20 ± 0.8</td>
<td>2.38 ± 1.1</td>
<td>2.18 ± 0.7</td>
<td>.532</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>1236 ± 747</td>
<td>988 ± 847</td>
<td>816 ± 494</td>
<td>NA</td>
<td>.03</td>
</tr>
<tr>
<td>NYHA FC IV</td>
<td>39 %</td>
<td>37 %</td>
<td>5 %</td>
<td>11%</td>
<td>.063</td>
</tr>
</tbody>
</table>

n = 20 pts

Better Correction of Hyponatremia


Etude EUPHORIA

n = 20 pts
Effect of Peripheral Ultrafiltration in ADHF

ADHF 40 pats

20 PUF 1 Session 8h

4,650 ml 2.5 kg

UF à 24h Weight Loss at 24h

2,838 ml 1.8 kg

20 Standard Care

RCT n = 40 pts

The Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure Trial

Bart BA et al, J Am Col Cardiol. 2005; 46: 2043-2046
Main Results of Fluid Removal

**Median Cumulative Fluid Removal, L**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>24 hrs</th>
<th>48 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>PUF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
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**Median Weight Lost, kg**

<table>
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<th>24 hr</th>
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<th>30 days</th>
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<tbody>
<tr>
<td>PUF</td>
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</tr>
<tr>
<td>Standard</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **PUF** vs. **Standard**
  - * p = 0.012
  - **p** = 0.001

**RCT n = 40 pts**

Ultrafiltration versus IV Diuretics for Patients Hospitalized for Acute Decompensated Congestive HF

RCT (200 patients ADHF)

Ultrafiltration versus IV Diuretics for Patients Hospitalized for Acute Decompensated Congestive HF

Weight Loss: Primary End Point

Critère de jugement primaire:
L'UF améliore la perte de poids à 48 H

Secondary Endpoint:
UF Deteriorates Temporarily Renal Function

$p >0.05$ at all time points
Secondary Endpoint: Faster Reduction of BNP Concentrations

Non Significant Reduction of Mortality

**Ultrafiltration Group**

- 9 (9.6%)
  - 3 due to HF
  - 1 acute renal failure
  - 5 unrelated to either HF or treatment

**Standard Care Group**

- 11 (11.6%)
  - 5 due to HF
  - 1 myocardial infarction
  - 3 unrelated to either HF or treatment
  - 2 unknown causes

Sustain Effect of UF
Significant Reduction of Rehospitalization

Patients free from rehospitalization (%)

Days

Standard care arm (28 events)

Ultrafiltration arm (16 events)

p = 0.037

Cardiorenal Rescue Study in Acute Decompensated Heart Failure


- ADHF 188 pats
- Ultrafiltration Group
  - Intervention 96hrs – 4 days
  - Day 4, 7, 30, 60
  - I ary Endpoint
  - II ary Endpoint

- Stepped Pharmacologic Group
  - 94 pats

CARdiorenal REScue Study in Acute Decompensated Heart Failure

Flowchart of the CARRESS-HF

Enrollment

Allocation

Allocated to stepped pharmacologic care (n=94)
  Received allocated intervention (n=94)
  Did not receive allocated intervention (n=0)

Allocated to Ultrafiltration (n=96)
  Received allocated intervention (n=88)
  Did not receive allocated intervention (n=8)

  Reasons:
  - 1 Patient withdrew consent
  - 4 MD decision
  - 3 Other: 1 SAE, 1 central line access issue, 1 infusion pressure issue

Primary Analysis: Day 4

Analyzed (n=94)
  Excluded from analysis (n=0)

  6 patients received UF during the first 7 days of index hospitalization
  2 of the 6 patients received UF prior to 96 hours.

Day 60 Follow-up

Lost to follow-up (n=4)

Allocated to Ultrafiltration (n=94)
  Received allocated intervention (n=94)
  Did not receive allocated intervention (n=0)

Primary Analysis: Day 4

Analyzed (n=92)
  Excluded from analysis (n=2)

  Reasons:
  - 1 patient missing baseline creatinine
  - 1 patient missing all post-baseline creatinine

Lost to follow-up (n=2)

# Stepped Pharmacologic Care Algorithm

<table>
<thead>
<tr>
<th>Current Dose</th>
<th>Suggested Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>loop (/day)</td>
<td>loop (/day)</td>
</tr>
<tr>
<td>thiazide</td>
<td>thiazide</td>
</tr>
<tr>
<td>A: ≤ 80</td>
<td>40 mg iv bolus+ 5 mg/hr</td>
</tr>
<tr>
<td>B: 81-160</td>
<td>80 mg iv bolus+ 10 mg/hr</td>
</tr>
<tr>
<td>C: 161-240</td>
<td>80 mg iv bolus+ 20 mg/hr</td>
</tr>
<tr>
<td>D: &gt; 240</td>
<td>80 mg iv bolus+ 30 mg/hr</td>
</tr>
</tbody>
</table>

Vascular access

Ultrafiltration can be performed through the use of two peripheral IV's, the combination of an extended length catheter placed in the antecubital fossa and a standard peripheral IV, or in some circumstances, a single dual lumen peripheral IV. While central venous access is not necessary, it is commonly acquired in patients hospitalized with acute decompensated heart failure - especially those who develop cardiorenal syndrome. During the screening process, the use of pulmonary artery venous catheters to resolve uncertainty regarding patient’s hemodynamic and volume status is encouraged. In these instances, ultrafiltration can be performed utilizing the introducer sheath or a triple lumen catheter according to the manufacturer’s specifications.
Ultrafiltration Group Care

Anticoagulation

In order to prevent clotting of the ultrafiltration circuit, patients should receive heparin to achieve a PTT 2.0 - 2.5 times normal. Therapeutic doses of enoxaparin may be used as an alternative.

Fluid removal rates and target to therapy

Ultrafiltration will be initiated at a fluid removal rate of 200 cc per hour and continued until the patient’s signs and symptoms of congestion have been optimized. A fluid removal rate of 200 cc per hour will result in 4.8 L of fluid removal in 24 hours and a net negative fluid balance of approximately 2.8 L assuming the patient adheres to the 2 L fluid restriction mandated per protocol.
Primary Endpoint:
Composite (bivariate) creatinine and weight loss (96hrs)

Changes from Baseline in Body Weight

Fluid Volume Removed

Changes from Baseline in Creatinine

## Secondary Endpoints

<table>
<thead>
<tr>
<th>End Point</th>
<th>Pharmacologic Therapy (N = 94)</th>
<th>Ultrafiltration (N = 94)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant body weight loss and renal improvement — no. (%)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 96 hr</td>
<td>20 (21)</td>
<td>16 (17)</td>
<td>0.62</td>
</tr>
<tr>
<td>At 7 days</td>
<td>20 (21)</td>
<td>18 (19)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>End Point</th>
<th>Pharmacologic Therapy (N = 94)</th>
<th>Ultrafiltration (N = 94)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in sodium from baseline to 96 hr — mmol/liter</td>
<td>0.0±3.6</td>
<td>-2.3±3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in hemoglobin from baseline to 96 hr — g/dl</td>
<td>0.38±0.76</td>
<td>-0.01±0.92</td>
<td>0.002</td>
</tr>
<tr>
<td>Change in cystatin C from baseline to 96 hr — mg/liter</td>
<td>0.14±0.52</td>
<td>0.22±0.52</td>
<td>0.37</td>
</tr>
<tr>
<td>Change in blood urea nitrogen from baseline to 96 hr — mg/dl</td>
<td>5.68±18.29</td>
<td>12.54±24.81</td>
<td>0.02</td>
</tr>
<tr>
<td>Change in glomerular filtration rate from baseline to 96 hr — ml/min/1.73 m²</td>
<td>1.67±10.94</td>
<td>0.93±14.60</td>
<td>0.66</td>
</tr>
</tbody>
</table>

| Change in troponine equivalent dose from admission to discharge — mg/day   | 1.2±11.99                    | 29.8±11.99               | <0.001  |
| Death — no. (%)                                                           | 13 (14)                      | 16 (17)                  | 0.55    |
| Hospitalization — no./total no. (%)                                       |                               |                          |         |
| For heart failure                                                         | 24/93 (26)                   | 23/90 (26)               | 0.97    |
| For any cause                                                             | 37/93 (40)                   | 46/90 (51)               | 0.12    |
| Unscheduled emergency department or clinic visit — no./total no. (%)      | 13/93 (14)                   | 19/90 (21)               | 0.21    |

KM Time to Death or Heart Failure Rehospitalization

## Serious Adverse Events

**Pharmacologic Therapy (N = 94)** | **Ultrafiltration (N = 94)**
--- | ---
Any | 54 (57) | 68 (72)
Heart failure | 28 (30) | 31 (33)
Other cardiovascular disorder | 5 (5) | 6 (6)
Renal failure | 14 (15) | 17 (18)
Anemia or thrombocytopenia | 5 (5) | 8 (9)
Catheter-site hemorrhage | 0 | 2 (2)
Electrolyte disorder* | 3 (3) | 0
Gastrointestinal hemorrhage | 3 (3) | 7 (7)
Pneumonia or other respiratory disorder | 6 (6) | 10 (11)
Sepsis, bacteremia, or cellulitis | 4 (4) | 8 (9)
Other | 19 (20) | 17 (18)

*CARRESS-HF*
**CONCLUSIONS**

In a randomized trial involving patients hospitalized for acute decompensated heart failure, worsened renal function, and persistent congestion, the use of a stepped pharmacologic-therapy algorithm was superior to a strategy of ultrafiltration for the preservation of renal function at 96 hours, with a similar amount of weight loss with the two approaches. Ultrafiltration was associated with a higher rate of adverse events. (Funded by the National Heart, Lung, and Blood Institute; ClinicalTrials.gov number, NCT00608491.)
Major Concerns with CARRESS-HF Study

- No diuretic test period prior entering randomization (no refractory test)
- Differences in patient characteristics at baseline
- No real protocol in ultrafiltration arm (200ml/hr over 3 days)
- Serious adverse events are essentially related to:
  - Uncontrolled fluid volume depletion in UF arm
  - Vascular access related complications (hemorrhage, infection, sepsis...)
  - Inadequate anticoagulation (gut hemorrhage)
  - Pneumonia from septic origin?
- Suboptimal use of isolated ultrafiltration (lack of cross talk cardio-nephro?)

What Next after CARRESS-HF Study?
Continuous Ultrafiltration for Congestive Heart Failure: the Cuore Trial

Early Start of SCUF Improves CHF Patient Outcomes

Cardiorenal Syndrome: More Opportunities for Therapy

ACE-ARBs
BB – CaB

Heart failure
Iron deficiency
Renal dysfunction

Anaemia
ESA Therapy

UF Mechanical natriuresis
Salt Restriction
Education
Diuretics...

Iron Supplementation

Macdougall IC et al, Europ J Heart Fail. 2012; 14:882-886
Stage D HF Resistant to Optimized Treatment...

Let's Do Slow Ultrafiltration
Several Trials are Still Ongoing
<table>
<thead>
<tr>
<th>Rank</th>
<th>Status</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unknown †</td>
<td>Treatment of Severe Heart Failure by Ultrafiltration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Condition: Severe Congestive Heart Failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention: Procedure: ultrafiltration</td>
</tr>
<tr>
<td>7</td>
<td>Recruiting</td>
<td>Study of Heart Failure Hospitalizations After Aquapheresis Therapy Compared to Intravenous (IV) Diuretic Treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conditions: Heart Failure; Cardiac Failure; Acute Decompensated Heart Failure (ADHF)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interventions: Device: Isolated veno-venous ultrafiltration (AQ); Drug: IV Loop Diuretics (LD)</td>
</tr>
<tr>
<td>9</td>
<td>Not yet recruiting</td>
<td>Feasibility Assessment of the Aquadex FlexFlow™ Ultrafiltration System in Treating Non Hospitalized Heart Failure Patients in Dedicated Heart Failure Centers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Condition: Heart Failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention: Procedure: blood ultrafiltration</td>
</tr>
<tr>
<td>12</td>
<td>Active, not recruiting</td>
<td>REWORD-HF REverse WOrsening Renal Function in Decompensated Heart Failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Condition: Acute Decompensated Heart Failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interventions: Drug: Furosemide or Furosemide and Dopamine; Device: Ultrafiltration</td>
</tr>
<tr>
<td>15</td>
<td>Recruiting</td>
<td>Slow Continuous Ultrafiltration Using Central vs Peripheral Line: Feasibility of Implementation, Safety and Efficacy in Acute Heart Failure Syndromes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Condition: Heart Failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interventions: Procedure: Peripheral line; Procedure: Central line vein</td>
</tr>
<tr>
<td>21</td>
<td>Not yet recruiting</td>
<td>Body Composition Monitor(BCM) Guided Fluid Management in Maintenance Hemodialysis (MHD) Patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Condition: End Stage Renal Disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interventions: Device: body bioimpedance spectroscopy device; Device: Device</td>
</tr>
</tbody>
</table>