Evidence-based practice in nephrology: Meta-analysis

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Synthesizing evidence

- Narrative reviews
- Systematic reviews
- Meta-analysis
- Decision analysis
- Cost-effectiveness analysis
- Clinical practice guidelines
Comparing systematic reviews with narrative “non-systematic” reviews

**Narrative Reviews**

- Give panoramic view, usually cover whole topic. Example: textbook chapters
- Emphasize “background” knowledge:
  - What causes the disorder?
  - What are the clinical manifestations?
  - What treatment options are available?
- Susceptible to bias in selecting, appraising and combining studies to answer questions

**Systematic Reviews**

- Give telescopic view, usually address one question or a few questions
- Focus on “foreground” knowledge: For example, in treating patients with this disorder, which of the two available treatments is better at improving clinical outcomes safely?
- Use rigorous methods to minimize bias and help improve reliability and accuracy of conclusions
- Can provide pooled estimates of treatment benefits and risks

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Semi-annual newsletter • VA Center of Excellence • San Antonio and Charleston • Fall 1998
Meta-Analysis
(Overview, Systematic Review)

• A scientific discipline which applies a protocol to critically evaluate and uses statistical methods to combine the results of (previous) research.

• Provides a quantitative summary of the overall treatment effect (typically an overall estimate and confidence interval).

• Increasingly being used to understand differences among studies to explain discrepancies of results and to generate hypotheses of interactions.

• To guide future research.
Clinical Applications of Meta-Analysis

- Epidemiology
  - To provide more reliable estimates of risks
- Diagnostic Test
  - To provide more reliable estimates of the diagnostic accuracy of tests
- Interventions
  - To estimate the efficacies and risks of treatments
Scope

AKI
- Epidemiology
- Biomarkers: L-FABP
- Intervention: Hypothermia, diuretic use

CKD
- Antihypertensive drugs: RAAS, CCB
- Bicarbonate treatment
- Initiation dialysis

HD
- Modality: convective and frequent HD
- Water treatment: ultrapure dialysate
- Anemia: intravenous iron therapy
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INTRODUCTION

- Over the last decade standardized definitions [1] have provided a uniform means to recognize and describe the epidemiology of AKI.
- The burden of AKI around the globe has not been systematically examined.
- A systematic review of large cohort studies was conducted to estimate the world incidence of AKI and its stages of severity and associated mortality, and to describe geographic variations according to countries, regions, and their economies.

METHODS

• Study selection
  – Prospective and retrospective cohort studies
  – Reports of incidence of AKI and associated outcomes
    • Dialysis requirement
    • Recovery of function
    • Short and long-term mortality
  – Adults (>18 years) minimum sample size 500
  – Children minimum sample size 50
METHODS

• Study selection
  – Data extraction by pairs of authors
    • Country, year of publication
    • Study design
    • Sample size
    • Patient demographics
    • Clinical setting
      – Hospital acquired
      – Community acquired
• AKI DEFINITION
• PATIENT OUTCOMES
  – Survival
  – Recovery of function (inconsistently reported)
METHODS

• Countries grouped within continents and world zones
  • Geoscheme by the United Nations Statistics Division
• Country economies
  – Four ranges of gross national income per capita
  • World Bank classification of income of economies

<table>
<thead>
<tr>
<th>COUNTRY INCOME</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW (LIC)</td>
<td>≤US$ 1005</td>
</tr>
<tr>
<td>LOWER MIDDLE (LMIC)</td>
<td>US$ 1006-$ 3975</td>
</tr>
<tr>
<td>UPPER MIDDLE (UMIC)</td>
<td>US$ 3976-$ 12275</td>
</tr>
<tr>
<td>HIGH (HIC)</td>
<td>US$ ≥12,276</td>
</tr>
</tbody>
</table>
METHODS

• Countries classified according to total national expenditure on health
  – Sum of general government and private health expenditures in a given year as a percentage of gross domestic product (GDP)
    • World Health Organization’s World Health Statistics

• Countries classified by latitude: North and South of the Equator
METHODS

- HARMONIZATION OF AKI DEFINITIONS
  - We first classified studies according to the KDIGO, RIFLE or AKIN criteria, other biochemical definitions, or dialysis requirement and ICD 9 or 10 administrative codes
  - We then redefined the AKI in the RIFLE or AKIN-defined studies by using the KDIGO definitions
  - Studies were then classified as
    - KDIGO or equivalent definition
    - Non-KDIGO definitions
METHODS

• DATA SYNTHESIS AND STATISTICAL ANALYSIS
  – Inter rate agreement by weighted Cohen’s κ coefficient
  – Random effects model meta-analysis to generate pooled incidence rates of AKI, stages and associated mortality
  – Random effects model meta-analysis to compute OR for mortality in AKI vs. Non-AKI patients
  – Heterogeneity by I² index and Q test P value
  – Random-effects subgroup and meta-regression analysis:
    • AKI rates and associated mortality
    • Geographic world regions
    • Patterns of country economies and latitude
In the pooled large cohort of 50,000,000 individuals worldwide, 1 in 5 adult and 1 in 3 children experienced AKI during a hospital care (KDIGO definitions)

Susantitaphong P, et al. CJASN 2013, June 6
No. studies: 110, 26, 25, 25, 31
No. subjects with AKI: 429,535, 8,226, 42,354, 42,354, 6,534

Susantitaphong P, et al. CJASN 2013, June 6
No. studies 92 21 20 20 20
No. subjects with AKI 405,616 90,048 40,631 38,914 4,427
No. subjects without AKI 1,765,574 1,127,070 1,120,523 1,120,523 127,969
Very few studies from LMIC, where 85% of the world population residents.

Susantitaphong P, et al. CJASN 2013, June 6
LITERATURE SEARCH
Pubmed, Web of Science
2012-2014

1049 citations

Excluded 549 citations

500 citations

187 papers
Did not meet meta-analysis criteria
(89,325 subjects)

Regional Analysis

Africa
62 studies
(55,309 Subjects)

Asia
92 studies
(26,993 Subjects)

Latin America
33 studies
(7,023 Subjects)

Lameire
Jha
Garcia-Garcia

313 papers
Met meta-analysis Criteria
(28,618,562 Subjects)

New Meta-analysis
765 studies
(77,393,454 Subjects)

Previous Meta-analysis
2004-2012
452 studies
(48,774,892 Subjects)

Cerda, Susantitaphong, Cruz, Jaber

AKI INCIDENCE BY KDIGO definition

LARGE INCREASE IN AKI REPORTING WITH KDIGO CRITERIA BETWEEN 2012 AND 2014

Northern America 22.3%
Central America
Caribbean
Northern Europe 19.3%
Western Europe 20.8%
Southern Europe 25.2%
Western Africa 1.7%
Northern Africa 0.7%
Southern Africa
Middle Africa
Eastern Africa 13.4%
Southern Asia 7.5%
Eastern Asia 19.4%
Southeastern Asia 31%
Australia and New Zealand 16.9%
Incidence and Mortality of AKI
By Country Income
Second Meta-Analysis 2004-2014

<table>
<thead>
<tr>
<th>REGION BY INCOME</th>
<th>INCIDENCE AKI (95% CI)</th>
<th>NUMBER OF STUDIES</th>
<th>MORTALITY AKI (95% CI)</th>
<th>NUMBER OF STUDIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMIC</td>
<td>16.1% (10.0-24.9)</td>
<td>42</td>
<td>30% (24.0-36.8)</td>
<td>35</td>
</tr>
<tr>
<td>HIC</td>
<td>21.9% (19.9-24.1)</td>
<td>215</td>
<td>19.3% (17.9-20.8)</td>
<td>136</td>
</tr>
</tbody>
</table>

Incidence and mortality of AKI in meta-analysis studies, distributed by country income.
LMIC: Low-middle income countries; HIC: High-income countries
* p=0.0644 by unpaired t-test; ** p=0.003 by unpaired t-test

Cerdá, Susantitaphong, Cruz and Jaber for the Oby25 Initiative
World Congress Nephrology 2015
Meta-regression analysis examining the association of AKI incidence rate and its associated mortality rate with aggregate study- and country-level characteristics:

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>RATE CHANGE (%)</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AKI INCIDENCE RATE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country percentage GDP spent on total health expenditure (per 1% ↑)</td>
<td>0.54</td>
<td>0.38, 0.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Country gross national income per capita (per $10,000 ↑)</td>
<td>0.65</td>
<td>0.25, 1.05</td>
<td>0.001</td>
</tr>
<tr>
<td>Year of study publication (per year ↑)</td>
<td>-1.38</td>
<td>-1.73, -1.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>AKI-ASSOCIATED MORTALITY RATE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country percentage GDP spent on total health expenditure (per 1% ↑)</td>
<td>-1.10</td>
<td>-1.64, -0.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Country gross national income per capita (per $10,000 ↑)</td>
<td>-2.22</td>
<td>-3.18, -1.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Year of study publication (per year ↑)</td>
<td>-1.50</td>
<td>-2.28, -0.72</td>
<td>0.002</td>
</tr>
</tbody>
</table>

CONCLUSIONS

• Our new analysis includes data from all regions of the world.

• In the last 2 years, studies increasingly utilize KDIGO or equivalent definitions, thus making measurements comparable between countries.

• The use of KDIGO or equivalent definitions is already making our understanding of AKI in those regions much more reliable.

• In LMIC, measured AKI incidence is becoming quantitatively accurate.

• Incidence in LMIC is similar to HIC, whereas mortality in LMIC is greater than HIC.

• In LMIC, mortality is inversely related to country GDP and %GDP invested in health care, suggesting that greater investment in health care may improve outcomes.
AKI
- Epidemiology
- **Biomarkers**: L-FABP
- Intervention: Hypothermia, diuretic use

CKD
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HD
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Performance of urinary liver-type fatty acid-binding protein in acute kidney injury: a meta-analysis

Table 3. Summary Accuracy of Urinary L-FABP for Outcome Prediction

<table>
<thead>
<tr>
<th>Outcome Prediction</th>
<th>No. of Studies</th>
<th>No. of Patients</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>DOR (95% CI)</th>
<th>P</th>
<th>I² Index</th>
<th>Q Test P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute kidney injury</td>
<td>7</td>
<td>687</td>
<td>74.5 (60.4-84.8)</td>
<td>77.6 (61.5-88.2)</td>
<td>2.69 (1.63-4.43)</td>
<td>&lt;0.001</td>
<td>41%</td>
<td>0.1</td>
</tr>
<tr>
<td>Dialysis requirement</td>
<td>3</td>
<td>436</td>
<td>69.1 (34.6-90.5)</td>
<td>42.7 (3.1-94.5)</td>
<td>2.24 (0.53-9.50)</td>
<td>0.3</td>
<td>36%</td>
<td>0.2</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>3</td>
<td>561</td>
<td>93.2 (66.2-99.0)</td>
<td>78.8 (27.0-97.4)</td>
<td>13.72 (1.96-95.89)</td>
<td>0.008</td>
<td>51%</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Note: Sensitivity and specificity are given as estimated percentages. Abbreviations: CI, confidence interval; DOR, diagnostic odds ratio; L-FABP, liver-type fatty acid-binding protein.

a Derived from random-effects model meta-analyses.
b Derived from bivariate-model meta-analysis.
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Scope
Therapeutic hypothermia and prevention of acute kidney injury: a meta-analysis of randomized controlled trials

Therapeutic hypothermia prevented neither the development of AKI nor dialysis requirement, but was associated with lower mortality.

A meta-analysis of continuous vs intermittent infusion of loop diuretics in hospitalized patients

Continuous infusion of loop diuretics preceded by a loading dose results in greater diuresis in hospitalized adults with extracellular fluid volume expansion compared with intermittent dosing regimens.

**Scope**

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### Efficacy and safety of combined vs. single renin-angiotensin-aldosterone system blockade in chronic kidney disease: a meta-analysis

#### Table 2. Summary effect of combined vs. single RAAS blockade therapy on kidney-related endpoints and blood pressure parameters in patients with chronic kidney disease

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>No. study arms</th>
<th>No. participants</th>
<th>Net change* (95% CI)</th>
<th>P-value</th>
<th>I² index† (Chi-square)</th>
<th>P-value</th>
<th>Egger test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urine albumin excretion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standardized</td>
<td>30</td>
<td>2,165</td>
<td>−0.435 (−0.717, −0.154)</td>
<td>0.002</td>
<td>88.7</td>
<td>&lt;0.001</td>
<td>0.212</td>
</tr>
<tr>
<td>Absolute (g/g of creatinine)</td>
<td>9</td>
<td>1,287</td>
<td>−0.090 (−0.145, −0.036)</td>
<td>0.001</td>
<td>72.0</td>
<td>&lt;0.001</td>
<td>NA</td>
</tr>
<tr>
<td>Absolute (g/day)</td>
<td>15</td>
<td>618</td>
<td>−0.032 (−0.061, −0.003)</td>
<td>0.030</td>
<td>72.0</td>
<td>&lt;0.001</td>
<td>NA</td>
</tr>
<tr>
<td>Absolute (g/g or g/day)</td>
<td>24</td>
<td>1,905</td>
<td>−0.062 (−0.097, −0.028)</td>
<td>&lt;0.001</td>
<td>90.0</td>
<td>&lt;0.001</td>
<td>0.898</td>
</tr>
<tr>
<td><strong>Urine protein excretion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standardized</td>
<td>56</td>
<td>2,257</td>
<td>−0.404 (−0.498, −0.309)</td>
<td>&lt;0.001</td>
<td>16.6</td>
<td>0.148</td>
<td>0.170</td>
</tr>
<tr>
<td>Absolute (g/g of creatinine)</td>
<td>10</td>
<td>697</td>
<td>−0.291 (−0.482, −0.099)</td>
<td>0.003</td>
<td>50.0</td>
<td>0.036</td>
<td>NA</td>
</tr>
<tr>
<td>Absolute (g/day)</td>
<td>45</td>
<td>1,440</td>
<td>−0.363 (−0.478, −0.247)</td>
<td>&lt;0.001</td>
<td>50.0</td>
<td>&lt;0.001</td>
<td>NA</td>
</tr>
<tr>
<td>Absolute (g/g or g/day)</td>
<td>55</td>
<td>2,137</td>
<td>−0.339 (−0.434, −0.243)</td>
<td>&lt;0.001</td>
<td>49.6</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Glomerular filtration rate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standardized</td>
<td>69</td>
<td>3,791</td>
<td>−0.094 (−0.171, −0.017)</td>
<td>0.016</td>
<td>19.8</td>
<td>0.082</td>
<td>0.525</td>
</tr>
<tr>
<td>Absolute (mL/min or mL/min/1.73m²)</td>
<td>58</td>
<td>2,734</td>
<td>−1.794 (−3.045, −0.544)</td>
<td>0.005</td>
<td>0</td>
<td>0.790</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Serum potassium</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standardized</td>
<td>61</td>
<td>2,982</td>
<td>0.278 (0.178, 0.377)</td>
<td>&lt;0.001</td>
<td>39.2</td>
<td>0.001</td>
<td>0.123</td>
</tr>
<tr>
<td>Absolute (mEq/L)</td>
<td>54</td>
<td>2,255</td>
<td>0.134 (0.089, 0.179)</td>
<td>&lt;0.001</td>
<td>36.2</td>
<td>0.005</td>
<td>0.358</td>
</tr>
<tr>
<td><strong>Systolic blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standardized</td>
<td>77</td>
<td>5,582</td>
<td>−0.336 (−0.404, −0.268)</td>
<td>&lt;0.001</td>
<td>22.7</td>
<td>0.044</td>
<td>0.175</td>
</tr>
<tr>
<td>Absolute (mmHg)</td>
<td>65</td>
<td>4,365</td>
<td>−3.755 (−4.579, −2.931)</td>
<td>&lt;0.001</td>
<td>12.8</td>
<td>0.197</td>
<td>0.584</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standardized</td>
<td>76</td>
<td>5,454</td>
<td>−0.279 (−0.363, −0.194)</td>
<td>&lt;0.001</td>
<td>47.4</td>
<td>&lt;0.001</td>
<td>0.181</td>
</tr>
<tr>
<td>Absolute (mmHg)</td>
<td>64</td>
<td>4,237</td>
<td>−2.214 (−3.116, −1.313)</td>
<td>&lt;0.001</td>
<td>73.2</td>
<td>&lt;0.001</td>
<td>0.777</td>
</tr>
<tr>
<td><strong>Mean arterial pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standardized</td>
<td>17</td>
<td>489</td>
<td>−0.179 (−0.358, −0.001)</td>
<td>0.049</td>
<td>0</td>
<td>0.677</td>
<td>0.212</td>
</tr>
<tr>
<td>Absolute (mmHg)</td>
<td>17</td>
<td>489</td>
<td>−1.718 (−3.100, −0.335)</td>
<td>0.015</td>
<td>0</td>
<td>0.778</td>
<td>0.185</td>
</tr>
</tbody>
</table>

* By random effects model meta-analysis †A measure of statistical heterogeneity across study results; an I² index ≥ 50% indicates medium-to-high heterogeneity.

Efficacy and safety of combined vs. single renin-angiotensin-aldosterone system blockade in chronic kidney disease: a meta-analysis

Table 3. Summary effect of combined vs. single RAAS blockade therapy on binary outcomes.

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Peto fixed-effect model</th>
<th>Random-effects model</th>
<th>Assessment of heterogeneity</th>
<th>Assessment of publication bias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. study arms</td>
<td>No. participants</td>
<td>Odds ratio (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Doubling of serum creatinine</td>
<td>17</td>
<td>2,998</td>
<td>0.796 (0.523, 1.211)</td>
<td>0.287</td>
</tr>
<tr>
<td>Development of hyperkalemia</td>
<td>35</td>
<td>4,205</td>
<td>2.176 (1.685, 2.810)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression to overt proteinuria</td>
<td>7</td>
<td>491</td>
<td>0.975 (0.534, 1.782)</td>
<td>0.935</td>
</tr>
<tr>
<td>Regression to normoalbuminuria</td>
<td>12</td>
<td>1,082</td>
<td>1.772 (1.320, 2.379)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Achievement of blood pressure goal</td>
<td>9</td>
<td>1,858</td>
<td>1.520 (1.169, 1.977)</td>
<td>0.002</td>
</tr>
<tr>
<td>Addition of other anti-hypertensive drugs</td>
<td>13</td>
<td>1,571</td>
<td>0.608 (0.459, 0.806)</td>
<td>0.001</td>
</tr>
<tr>
<td>Withdrawal of anti-hypertensive drugs</td>
<td>5</td>
<td>882</td>
<td>0.855 (0.488, 1.496)</td>
<td>0.582</td>
</tr>
<tr>
<td>Any adverse effect*</td>
<td>13</td>
<td>2,518</td>
<td>0.901 (0.747, 1.086)</td>
<td>0.275</td>
</tr>
<tr>
<td>Subject drop-out</td>
<td>20</td>
<td>1,965</td>
<td>1.151 (0.739, 1.792)</td>
<td>0.533</td>
</tr>
<tr>
<td>Development of hypotension</td>
<td>22</td>
<td>1,890</td>
<td>3.990 (2.649, 6.009)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>4</td>
<td>246</td>
<td>2.958 (0.893, 9.803)</td>
<td>0.076</td>
</tr>
<tr>
<td>Mortality</td>
<td>5</td>
<td>1,711</td>
<td>0.384 (0.061, 2.396)</td>
<td>0.305</td>
</tr>
</tbody>
</table>

* As defined in the individual studies
Scope

AKI
- Epidemiology
- Biomarkers: L-FABP
- Intervention: Hypothermia, diuretic use

CKD
- Antihypertensive drugs: RAAS
- Bicarbonate treatment
- Initiation dialysis

HD
- Modality: convective and frequent HD
- Water treatment: ultrapure dialysate
- Anemia: intravenous iron therapy
Alkali therapy is associated with an improvement in kidney function, which may afford a long-term benefit in slowing the progression of CKD. However, differences in study protocols and small sample sizes preclude definitive conclusions.
**Scope**

**AKI**
- Epidemiology
- Biomarkers: L-FABP
- Intervention: Hypothermia, diuretic use

**CKD**
- Antihypertensive drugs: RAAS
- Bicarbonate treatment
- **Initiation dialysis**

**HD**
- Modality: convective and frequent HD
- Water treatment: ultrapure dialysate
- Anemia: intravenous iron therapy
Glomerular Filtration Rate at Initiation of Dialysis and Mortality in Chronic Kidney Disease: A Meta-analysis

Susantitaphong, et al AJKD 2012
Citations identified from electronic database search
MEDLINE: 2,792
ClinicalTrials.gov: 1,082
Cochrane Central Register of Controlled Trials: 60
American Society of Nephrology abstracts: 18

Excluded on the basis of title and abstract review (n = 3,895)

Potentially eligible and requiring full-text analysis (n = 39)

Excluded on the basis of full-text review of article (n = 22)
No outcomes of interest: 11
Narrative reviews/letters: 7
Case series: 1
No measures of kidney function: 2
Age < 18 years: 1

Studies included in the systematic review (n = 17; 1,081,116 patients)
Randomized controlled trial: 1
Cohort studies: 16

Studies included in the meta-analysis of GFR and mortality (n = 14; 1,079,917 patients)
Cohort studies: 14 (representing 15 cohorts)

Susantitaphong, et al AJKD 2012
A Randomized, Controlled Trial of Early versus Late Initiation of Dialysis

Kaplan–Meier Curves for Time to Death

Hazard ratio, 1.04 (95% CI, 0.83–1.30)  
P=0.75

No. at Risk
Early start 404 358 305 249 177 99 59 32
Late start 424 385 333 254 187 115 60 32

Cooper et al. NEJM 2010
GFR at initiation of dialysis and mortality in CKD: a meta-analysis

A. Adjusted HR for all-cause mortality (per 1 ml/min/1.73 m² GFR increment)

Excluded
- No. cohort studies: 6
- No. patients: 42,808

Included
- No. cohort studies: 9
- No. patients: 1,037,109

Nutritional covariates

B. Adjusted HR for all-cause mortality (per 1 ml/min/1.73 m² GFR increment)

HD
- No. cohort studies: 5
- No. patients: 139,797

PD
- No. cohort studies: 4
- No. patients: 2,820

Susantitaphong, et al AJKD 2012
Scope

AKI
- Epidemiology
- Biomarkers: L-FABP
- Intervention: Hypothermia, diuretic use

CKD
- Antihypertensive drugs: RAAS, CCB
- Bicarbonate treatment
- Initiation dialysis

HD
- Modality: convective and frequent HD
- Water treatment: ultrapure dialysate
- Anemia: intravenous iron therapy
Convective therapies versus low-flux hemodialysis for chronic kidney failure: a meta-analysis of randomized controlled trials

Table 2. Summary effect of convective therapies versus low-flux hemodialysis on the binary outcomes of interest

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>No. of convective therapy study arms</th>
<th>No. of patients</th>
<th>Relative risk (95% confidence interval)</th>
<th>P value</th>
<th>Assessment of heterogeneity</th>
<th>Assessment of publication bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>21</td>
<td>4766</td>
<td>0.881 (0.759, 1.024)</td>
<td>0.09</td>
<td>18%</td>
<td>0.22</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>3</td>
<td>3207</td>
<td>0.835 (0.711, 0.980)</td>
<td>0.03</td>
<td>0%</td>
<td>0.97</td>
</tr>
<tr>
<td>Infection-related mortality</td>
<td>2</td>
<td>2493</td>
<td>0.913 (0.716, 1.163)</td>
<td>0.46</td>
<td>0%</td>
<td>0.60</td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td>10</td>
<td>3952</td>
<td>0.912 (0.824, 1.011)</td>
<td>0.08</td>
<td>78%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Therapy-related hypotension</td>
<td>12</td>
<td>1006</td>
<td>0.550 (0.347, 0.872)</td>
<td>0.01</td>
<td>99%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*A measure of statistical heterogeneity across study results; an $I^2$ index ≥ 50% indicates medium-to-high heterogeneity.

Table 3. Summary effect of convective therapies versus low-flux hemodialysis on the removal of solutes in crossover and parallel-arm trials combined

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>No. of convective therapy study arms</th>
<th>No. of patients</th>
<th>Absolute mean net change (95% CI)</th>
<th>P value</th>
<th>Assessment of heterogeneity</th>
<th>Assessment of publication bias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Low-molecular-weight solutes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea (60 Da)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-therapy serum level, mg/dL</td>
<td>14</td>
<td>2329</td>
<td>-0.53 (2.24, 1.18)</td>
<td>0.54</td>
<td>0.22</td>
<td>0.92</td>
</tr>
<tr>
<td>Reduction ratio, %</td>
<td>25</td>
<td>2796</td>
<td>0.65 (0.52, 1.81)</td>
<td>0.28</td>
<td>0.06</td>
<td>0.76</td>
</tr>
<tr>
<td>Kt/V</td>
<td>46</td>
<td>4989</td>
<td>0.03 (-0.01, 0.07)</td>
<td>0.09</td>
<td>0.04</td>
<td>0.01</td>
</tr>
<tr>
<td>Clearance, mL/min</td>
<td>7</td>
<td>2064</td>
<td>23.41 (7.26, 39.56)</td>
<td>0.005</td>
<td>0.50</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Creatinine (113 Da)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-therapy serum level, mg/dL</td>
<td>11</td>
<td>423</td>
<td>-0.03 (0.38, 0.33)</td>
<td>0.87</td>
<td>0</td>
<td>0.57</td>
</tr>
<tr>
<td>Reduction ratio, %</td>
<td>14</td>
<td>562</td>
<td>1.54 (1.08, 4.16)</td>
<td>0.25</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Clearance, mL/min</td>
<td>6</td>
<td>204</td>
<td>19.63 (11.86, 27.40)</td>
<td>&lt;0.001</td>
<td>0.70</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Uric acid (168 Da)</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pre-therapy serum level, mg/dL</td>
<td>3</td>
<td>62</td>
<td>-0.53 (1.45, 0.40)</td>
<td>0.26</td>
<td>0.07</td>
<td>0.58</td>
</tr>
<tr>
<td>Reduction ratio, %</td>
<td>3</td>
<td>102</td>
<td>0.15 (2.46, 2.77)</td>
<td>0.91</td>
<td>0</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>Phosphate (120 Da)</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Pre-therapy serum level, mg/dL</td>
<td>13</td>
<td>1347</td>
<td>-0.20 (0.42, 0.03)</td>
<td>0.08</td>
<td>0.42</td>
<td>0.05</td>
</tr>
<tr>
<td>Reduction ratio, %</td>
<td>11</td>
<td>442</td>
<td>8.56 (5.46, 11.66)</td>
<td>&lt;0.001</td>
<td>0.95</td>
<td>0.97</td>
</tr>
<tr>
<td>Clearance, mL/min</td>
<td>5</td>
<td>196</td>
<td>20.75 (12.34, 29.17)</td>
<td>&lt;0.001</td>
<td>0.48</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>Asymmetric dialyzer (202 Da)</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-therapy serum level, μmol/L</td>
<td>3</td>
<td>183</td>
<td>-0.06 (0.18, 0.06)</td>
<td>0.36</td>
<td>0.21</td>
<td>0.76</td>
</tr>
<tr>
<td>Reduction ratio, %</td>
<td>3</td>
<td>112</td>
<td>-1.59 (6.04, 2.86)</td>
<td>0.48</td>
<td>0.58</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>Middle-sized solutes</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Beta-2 microglobulin (11,818 Da)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-therapy serum level, mg/dL</td>
<td>26</td>
<td>4194</td>
<td>-9.94 (12.42, -7.46)</td>
<td>&lt;0.001</td>
<td>88</td>
<td>0.001</td>
</tr>
<tr>
<td>Reduction ratio, %</td>
<td>31</td>
<td>970</td>
<td>60.80 (51.09, 70.32)</td>
<td>&lt;0.001</td>
<td>97</td>
<td>0.001</td>
</tr>
<tr>
<td>Clearance, mL/min</td>
<td>9</td>
<td>2038</td>
<td>64.77 (46.76, 82.78)</td>
<td>&lt;0.001</td>
<td>99</td>
<td>0.001</td>
</tr>
<tr>
<td>Removal, mg/session</td>
<td>5</td>
<td>164</td>
<td>205.12 (153.89, 256.36)</td>
<td>&lt;0.001</td>
<td>0.90</td>
<td>0.06</td>
</tr>
<tr>
<td>Leptin (16 000 Da)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Pre-therapy serum level, μg/L</td>
<td>4</td>
<td>87</td>
<td>-6.16 (18.31, 5.99)</td>
<td>0.32</td>
<td>0.34</td>
<td>0.05</td>
</tr>
<tr>
<td>Reduction ratio, %</td>
<td>9</td>
<td>108</td>
<td>23.91 (15.66, 32.17)</td>
<td>&lt;0.001</td>
<td>17</td>
<td>0.29</td>
</tr>
</tbody>
</table>

**Table 3. Continued**

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>No. of convective therapy study arms</th>
<th>No. of patients</th>
<th>Absolute mean net change (95% CI)</th>
<th>P value</th>
<th>Assessment of heterogeneity</th>
<th>Assessment of publication bias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Parathyroid hormone (9225 Da)</td>
<td></td>
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<td></td>
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<tr>
<td>Pre-therapy serum level, pg/mL</td>
<td>11</td>
<td>1192</td>
<td>-20.74 (14.56, -4.08)</td>
<td>0.10</td>
<td>0.09</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>Vitamin B12 (1337 Da)</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Pre-therapy serum level, pmol/L</td>
<td>2</td>
<td>93</td>
<td>-18.09 (52.58, 16.41)</td>
<td>0.30</td>
<td>0.01</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>Protein-bound solutes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homocysteine (135 Da)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-therapy serum level, mg/dL</td>
<td>10</td>
<td>592</td>
<td>-1.97 (3.67, -2.77)</td>
<td>0.02</td>
<td>0.13</td>
<td>0.93</td>
</tr>
<tr>
<td>Reduction ratio, %</td>
<td>7</td>
<td>354</td>
<td>4.09 (1.51, 6.67)</td>
<td>0.02</td>
<td>0.13</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Advanced glycation end-products (284 Da)</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Reduction ratio, %</td>
<td>4</td>
<td>181</td>
<td>22.80 (11.09, 34.52)</td>
<td>&lt;0.001</td>
<td>0.88</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>3-Carboxy-4-methyl-5-propyl-2-furanpropionic acid (240 Da)</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pre-therapy serum level, mg/dL</td>
<td>2</td>
<td>42</td>
<td>-0.15 (0.34, 0.04)</td>
<td>0.12</td>
<td>0.01</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>Indole acetic acid (175 Da)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-therapy serum level, mg/dL</td>
<td>2</td>
<td>42</td>
<td>-0.04 (0.17, 0.10)</td>
<td>0.60</td>
<td>62</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Indoxyl sulfate (251 Da)</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-therapy serum level, mg/dL</td>
<td>2</td>
<td>42</td>
<td>-0.42 (0.91, 0.07)</td>
<td>0.09</td>
<td>0</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>Hippuric acid (179 Da)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-therapy serum level, mg/dL</td>
<td>2</td>
<td>42</td>
<td>-0.94 (2.62, 0.74)</td>
<td>0.27</td>
<td>0</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Pentosidine (342 Da)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-therapy serum free-form level, pmol/mL</td>
<td>5</td>
<td>210</td>
<td>-15.67 (15.32, 3.01)</td>
<td>0.001</td>
<td>42</td>
<td>0.14</td>
</tr>
<tr>
<td>Pre-therapy serum protein-bound form level, mmol/mg</td>
<td>6</td>
<td>232</td>
<td>-5.41 (0.86, -2.75)</td>
<td>&lt;0.001</td>
<td>16</td>
<td>0.31</td>
</tr>
<tr>
<td>Reduction ratio, %</td>
<td>3</td>
<td>74</td>
<td>0.12 (-7.91, 7.84)</td>
<td>0.98</td>
<td>33</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Advanced oxidation protein products (600 000 Da)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-therapy serum level, μmol/L</td>
<td>2</td>
<td>140</td>
<td>-18.43 (19.42, 12.57)</td>
<td>0.24</td>
<td>0.40</td>
<td>0.20</td>
</tr>
</tbody>
</table>

*Random-effects model meta-analysis

*A measure of statistical heterogeneity across study arms; an I² index ≥ 50% indicates medium-to-high heterogeneity.
Understanding discordant meta-analyses of convective dialytic therapies for chronic kidney failure

<table>
<thead>
<tr>
<th>Table 1. Summary of Findings From 4 Meta-analyses on the Efficacy of Convective Therapies for the Treatment of Chronic Kidney Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
</tr>
<tr>
<td><strong>Data sources</strong></td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
</tr>
<tr>
<td><strong>No. of RCTs (sample size)</strong></td>
</tr>
<tr>
<td><strong>Analytical approach</strong></td>
</tr>
<tr>
<td><strong>Results</strong></td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
</tr>
<tr>
<td><strong>Cardiovascular mortality</strong></td>
</tr>
<tr>
<td><strong>Therapy-related hypotension</strong></td>
</tr>
<tr>
<td><strong>β₂-Microglobulin clearance (mL/min)</strong></td>
</tr>
<tr>
<td><strong>Pre-treatment</strong></td>
</tr>
</tbody>
</table>

Note: The I² index is a measure of statistical heterogeneity across study results; I² index ≥ 75% indicates medium to high heterogeneity.
Abbreviations: ASN, American Society of Nephrology; CI, confidence interval; CINAHL, Cumulative Index to Nursing and Allied Health Literature; ESRD, end-stage renal disease; HD, hemodialysis; MD, mean difference; NR, not reported; RCT, randomized controlled trial; RR, relative risk.

*aPercentage of treatment sessions associated with hypotension.

*Post-treatment.

Effect of frequent or extended hemodialysis on cardiovascular parameters: a meta-analysis

Conversion from conventional to frequent or extended HD is associated with improvements in cardiac morphology and function, including LVMI and LV ejection fraction, respectively, and several blood pressure parameters, which collectively might confer long-term cardiovascular benefit. Trials with long-term clinical outcomes are needed.
Scope

AKI
- Epidemiology
- Biomarkers: L-FABP
- Intervention: Hypothermia, diuretic use

CKD
- Antihypertensive drugs: RAAS, CCB
- Bicarbonate treatment
- Initiation dialysis

HD
- Modality: convective and frequent HD
- Water treatment: ultrapure dialysate
- Anemia: intravenous iron therapy
Effect of ultrapure dialysate on markers of inflammation, oxidative stress, nutrition and anemia parameters: a meta-analysis

Table 2. Summary effect of ultrapure dialysate in cohorts (single-arm studies) and experimental study arms on markers of inflammation, oxidative stress, nutrition and anemia parameters

<table>
<thead>
<tr>
<th>Outcome variables</th>
<th>No. study arms</th>
<th>No. patients</th>
<th>Baseline mean value (95% CI)</th>
<th>Mean changea (95% CI)</th>
<th>P-value</th>
<th>Heterogeneity</th>
<th>Publication bias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>I² indexb (%)</td>
<td>Egger test P-value</td>
</tr>
<tr>
<td>Inflammatory markers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Q statistic P-value</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>23</td>
<td>2221</td>
<td>8.63 (6.62, 10.64)</td>
<td>-3.19 (-4.62, -1.75)</td>
<td>&lt;0.001</td>
<td>97</td>
<td>&lt;0.001 0.092</td>
</tr>
<tr>
<td>Interleukin-6, pg/mL</td>
<td>16</td>
<td>721</td>
<td>25.65 (20.81, 30.48)</td>
<td>-5.43 (-8.38, -2.48)</td>
<td>&lt;0.001</td>
<td>94</td>
<td>&lt;0.001 0.036</td>
</tr>
<tr>
<td>Interleukin-1 receptor antagonist, ng/mL</td>
<td>7</td>
<td>213</td>
<td>0.89 (0.42, 1.35)</td>
<td>-0.16 (-0.26, -0.06)</td>
<td>0.002</td>
<td>82</td>
<td>&lt;0.001 0.370</td>
</tr>
<tr>
<td>Tumor necrosis factor-α, pg/mL</td>
<td>8</td>
<td>256</td>
<td>34.58 (20.01, 49.16)</td>
<td>-13.29 (-22.06, -4.51)</td>
<td>0.003</td>
<td>93</td>
<td>&lt;0.001 0.222</td>
</tr>
<tr>
<td>Endotoxin, EU/mL</td>
<td>3</td>
<td>264</td>
<td>0.39 (0.01, 0.76)</td>
<td>-0.25 (-0.52, 0.01)</td>
<td>0.058</td>
<td>97</td>
<td>&lt;0.001 0.297</td>
</tr>
<tr>
<td>β2-microglobulin, mg/dL</td>
<td>5</td>
<td>460</td>
<td>35.80 (32.30, 39.30)</td>
<td>-3.09 (-4.97, -1.21)</td>
<td>0.001</td>
<td>80</td>
<td>&lt;0.001 0.582</td>
</tr>
<tr>
<td>Oxidative stress markers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentosidine, nmol/L</td>
<td>2</td>
<td>200</td>
<td>1537.79 (1488.95, 1586.63)</td>
<td>-263.76 (-330.69, -196.83)</td>
<td>&lt;0.001</td>
<td>0</td>
<td>0.764 NA</td>
</tr>
<tr>
<td>Myeloperoxidase, ng/mL</td>
<td>2</td>
<td>168</td>
<td>136.85 (110.93, 162.77)</td>
<td>-66.05 (-93.87, -38.22)</td>
<td>&lt;0.001</td>
<td>0</td>
<td>0.527 NA</td>
</tr>
<tr>
<td>Oxidized LDL cholesterol, U/L</td>
<td>2</td>
<td>160</td>
<td>51.60 (35.04, 68.17)</td>
<td>-6.90 (-12.88, -0.93)</td>
<td>0.024</td>
<td>48</td>
<td>0.166 NA</td>
</tr>
<tr>
<td>Nutritional markers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>14</td>
<td>1657</td>
<td>3.85 (3.75, 3.94)</td>
<td>0.11 (0.02, 0.19)</td>
<td>0.011</td>
<td>84</td>
<td>&lt;0.001 0.827</td>
</tr>
<tr>
<td>Anemia parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>11</td>
<td>1301</td>
<td>10.60 (10.07, 11.13)</td>
<td>0.40 (0.06, 0.75)</td>
<td>0.022</td>
<td>97</td>
<td>&lt;0.001 0.013</td>
</tr>
<tr>
<td>Ferritin, ng/mL</td>
<td>7</td>
<td>1028</td>
<td>378.22 (246.25, 510.19)</td>
<td>-25.79 (-69.42, 17.84)</td>
<td>0.247</td>
<td>99</td>
<td>&lt;0.001 0.286</td>
</tr>
<tr>
<td>TSAT, %</td>
<td>4</td>
<td>177</td>
<td>33.71 (32.24, 35.18)</td>
<td>-1.81 (-4.68, 1.07)</td>
<td>0.218</td>
<td>0</td>
<td>0.630 0.01</td>
</tr>
<tr>
<td>Erythropoietin dose, units/week</td>
<td>15</td>
<td>1455</td>
<td>5776 (4739, 6814)</td>
<td>-273 (-420, -126)</td>
<td>&lt;0.001</td>
<td>81</td>
<td>&lt;0.001 0.120</td>
</tr>
</tbody>
</table>

- Use of ultrapure dialysate in hemodialysis patients results in a decrease in markers of inflammation and oxidative stress, an increase in serum albumin and hemoglobin and a decrease in erythropoietin requirement.
- Although improvement in these surrogate endpoints might confer a cardiovascular benefit, a large trial with hard clinical endpoints is required.

Scope

AKI
• Epidemiology
• Biomarkers: L-FABP
• Intervention: Hypothermia, diuretic use

CKD
• Antihypertensive drugs: RAAS, CCB
• Bicarbonate treatment
• Initiation dialysis

HD
• Modality: convective and frequent HD
• Water treatment: ultrapure dialysate
• Anemia: intravenous iron therapy
Use of iron to treat anemia in CKD

TREATMENT WITH IRON AGENTS

• 2.1.1: When prescribing iron therapy, balance the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia-related symptoms against the risks of harm in individual patients (e.g., anaphylactoid and other acute reactions, unknown long-term risks). (Not Graded)

• 2.1.2: For adult CKD patients with anemia not on iron or ESA therapy we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (2C):

: an increase in Hb concentration without starting ESA treatment is desired* and TSAT is ≤ 30% and ferritin is ≤ 500 ng/ml (≤ 500 µg/l)

*Based on patient symptoms and overall clinical goals, including avoidance of transfusion, improvement in anemia-related symptoms, and after exclusion of active infection

KDIGO Guideline for Anemia. Kidney Int. vol 2 Issue 4, August 2012
Efficacy and safety of intravenous iron therapy for functional iron deficiency anemia in hemodialysis patients: a meta-analysis

- Intravenous iron therapy for functional iron deficiency anemia in hemodialysis patients improves anemia parameters but exerts some effects on markers of oxidative stress that are of unclear clinical significance.
- The long term safety and efficacy of this treatment strategy requires further study.

Thank you very much
Special thanks for all.

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