Mortality in chronic kidney failure: how to decrease it

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Kidney disease 1

Epidemiology, contributors to, and clinical trials of mortality risk in chronic kidney failure

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**What is chronic kidney failure (CKF)?**

**KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease**

<table>
<thead>
<tr>
<th>GFR categories (ml/min/1.73 m²)</th>
<th>Description and range</th>
<th>Persistent albuminuria categories Description and range</th>
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</thead>
<tbody>
<tr>
<td>G1</td>
<td>Normal or high</td>
<td>A1: Normal to mildly increased</td>
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<td></td>
<td></td>
<td>A2: Moderately increased</td>
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<td></td>
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<td>A3: Severely increased</td>
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<tr>
<td>G2</td>
<td>Mildly decreased</td>
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<td></td>
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<tr>
<td>G3a</td>
<td>Mildly to moderately decreased</td>
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<tr>
<td>G3b</td>
<td>Moderately to severely decreased</td>
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<tr>
<td>G4</td>
<td>Severely decreased</td>
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<tr>
<td>G5</td>
<td>Kidney failure</td>
<td></td>
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</tbody>
</table>

- **eGFR < 15 ml/min/1.73 m²**
- **GFR category G5**
- **KDOQI CKD stage 5**

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

*Kidney Int suppl 2013*
CVD mortality in CKF patients on RRT

Females
Males

Why?

Foley AJKD
• Are cardiovascular diseases the most frequent causes of death in CKF?

• What factors may contribute to the high mortality?

• What interventions decrease mortality?
Global causes of death in CKF

Each year 440,000 incident patients start RRT and 3,200,000 die without access to RRT

Death because RRT not available

Other causes of death

No RRT

Ortiz et al. Lancet 2014

CKF patient flow

Developed countries
(440000 incident patients/year)

- CKF
  - No RRT
  - RRT
    - D
      - 8% Tx

Yearly mortality:
- 5-20 %
- 1.5-7 %

Causes:
- 40 % CV
- 40 % CV

Emerging countries
(3200000 incident patients/year)

- CKF
  - No RRT
  - RRT
    - Dialysis
  - <1% Tx

Yearly mortality:
- 100 %
- 50-70 %

Causes:
- 25-70 % stop RRT

Ortiz et al. Lancet 2014
CKF is one of the fastest growing causes of mortality worldwide

% increase in death rate from CKF (1990-2010)

- World
- South America
- Caribbean
- Andean
- Tropical South America

+80%

CKF is one of the fastest growing causes of mortality worldwide.

• Are cardiovascular diseases the most frequent causes of death in ESRD?

• What factors may contribute to the high mortality?

• What interventions decrease mortality?

   Access to RRT
   (transplantation if possible)
• Are cardiovascular diseases the most frequent causes of death in ESRD?

• What factors may contribute to the high mortality?

• What interventions decrease mortality?
Causes of death in patients undergoing RRT

Global causes of death in CKF

Developed countries: ERA-EDTA

Non-cardiovascular, no-social
Cardiovascular
Social death

Ortiz et al. Lancet 2014

de Jager DJ et al. JAMA 2009; 302: 1782–89
Causes of death in patients undergoing RRT

Developed countries: ERA-EDTA

Global causes of death in CKF

No RRT

Cardiovascular
Social death
Non-cardiovascular, no-social
Unknown
Infection
Cancer
Cachexia
Miscellaneous

Ortiz et al. Lancet 2014

de Jager DJ et al. JAMA 2009; 302: 1782–89
Causes of death in patients undergoing RRT: geographical differences

Causes of death in patients receiving RRT. Developed countries

Global causes of death in CKF

Causes of death in patients receiving RRT. Ethiopian dialysis unit.

No RRT

Cardiovascular
Social death
Non-cardiovascular, no-social
Unknown
Infection
Cancer
Cachexia
Miscellaneous

Ortiz et al. Lancet 2014
Shibiru T et al. BMC Nephrol 2013; 14: 127
Causes of death in patients undergoing RRT according to age. ERA-EDTA

% of all deaths in the age group

Cardiovascular
Non-cardiovascular, non social
Social death
Unknown

Age group
de Jager DJ et al. JAMA 2009; 302: 1782–89
Causes of death in patients undergoing RRT according to age

Fold-change excess mortality in CKF on RRT vs general population, ERA-EDTA Registry

Ortiz et al. Lancet 2014
de Jager DJ et al. *JAMA* 2009; 302: 1782–89
Fold-change vs absolute excess mortality rate in CKF on RRT vs general population, ERA-EDTA

The highest excess mortality rate is found in the elderly: is this unavoidable?

Ortiz et al. Lancet 2014

de Jager DJ et al. JAMA 2009; 302: 1782–89
Absolute excess mortality rate vs absolute number of excess deaths in CKF on RRT vs general population, ERA-EDTA Registry

NON-cardiovascular causes are the real killers in CKF.... Specially in the elderly

Ortiz et al. Lancet 2014

de Jager DJ et al. JAMA 2009; 302: 1782–89
• Are cardiovascular diseases the most frequent causes of death in ESRD?

• **What factors may contribute to the high mortality?**

• What interventions decrease mortality?
Common risk factors
- Atherosclerosis
- Ischemia

Kidney failure
- Arteriosclerosis: arterial stiffness
- Diastolic dysfunction, LVH

Replacement of renal function?
- No RRT
- Dialysis: insufficient correction of some renal functions
- Transplantation: partial/full correction of all renal functions

Death

Dialysis-related factors
- Approx 2% of deaths are therapy-related

Transplantation-related factors
- Ortiz et al. Lancet 2014

Lowered risk
- Increased risk
- Certain consequence
Factors associated with increased mortality in patients on dialysis in observational studies

- Factors related to **dialysis initiation** (pre-dialysis care standards)
  - Late referral to nephrologist and sparse visits before dialysis initiation
  - Return to dialysis from transplantation
  - Poor planning for dialysis initiation
  - **First three months** in haemodialysis

- Factors potentially related to **dialysis care logistics**
  - Small dialysis facilities
  - Less **patient-doctor contact** and higher nephrologist **caseload**
  - **Shorter dialysis** session length (treatment time) in thrice weekly HD
  - **Day** following the long inter-haemodialysis interval
  - And others
Factors associated with increased mortality in patients on dialysis in *observational* studies (cont)

- Factors related to the **standard of care** on dialysis
  
  Central venous *catheter* use

  Abnormal **CKD-MBD parameters**, including high serum calcium, high serum phosphate, high PTH, high alkaline phosphatase, hypomagnesemia, bone fractures and cardiovascular calcification

  **CKD-MBD-relared?**

  Lower *predialysis* midweek *predialysis* **bicarbonate** > 27 mEq/L or ≤17 mEq/L

  Dialysate composition: High **dialysate bicarbonate**, low **dialysate calcium** or **potassium**

  Lower *predialysis* serum **sodium** or large interdialytic **weight gain** and high ultrafiltration rates
Factors associated with increased mortality in patients on dialysis in observational studies (cont II)

Factors related to the standard of care in patients on dialysis

**Therapeutic nihilism** or patient non-compliance

- No use of beta-blockers in patients without a previous history of heart failure
- No use of diuretics
- No use of vitamin D receptor activators (in some adjusted models)
- No use of phosphate binders
- No use of water soluble vitamins
- No use of monitored intradialytic oral nutritional supplements in patients on haemodialysis with albumin levels ≤3.5 g/dL

  Too low or too high HbA1C levels in diabetics on haemodialysis
  (<7.0/>7.9% or <5.4/>8.5%)

Protein-energy **wasting**

Loss of **residual renal function**

Pneumonia, **septicaemia or bacteraemia**, Inflammation
• Are cardiovascular diseases the most frequent causes of death in ESRD?

• What factors may contribute to the high mortality?

• What interventions decrease mortality?
Interventions tested in RCTs in CKF patients

• **May decrease mortality**
  – Choice of phosphate binder
  – HDF online
  – Carvedilol in patients on haemodialysis with severe heart failure
  – ACEI + ARB; spironolactone

• **Do not appear to decrease mortality**
  – Statins
  – Normalization of Hb (attempts at)
  – Earlier dialysis or higher conventional dialysis dose
  – Antioxidants
  – Antiplatelets
  – Cinacalcet
  – Intradialytic parenteral nutrition

• Few trials directly tested measures aimed at decreasing non-cardiovascular mortality
Take home message

• Excess mortality in CKF not only from cardiovascular causes

• Need to provide low-cost RRT for developing countries and to promote transplantation

• Need to understand the underlying causes and design multipronged approaches (the “Steno” approach)
  – To address different causes of CVD mortality
  – To address non-CVD mortality