Nephro Update Europe 2019

20 – 21 September, Prague

Hemodialysis, Nutrition & Medical Therapy in Hemodialysis Patients

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Methods

- Papers published in 2018-19
- Selection from:
  - Major medical journals (NEJM, Lancet, JAMA, Ann Int Med)
  - Major nephrology journals (NDT, JASN, cJASN, KI, AJKD)
- Topics:
  - Anemia
  - Dialysis in older adults
  - Cachexia
  - Guideline for vascular access care

Anemia

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The PIVOTAL Study

Intravenous Iron in Patients Undergoing Maintenance Hemodialysis

Macdougall et al. N Engl J Med. 2019 Jan 31;380(5):447-458

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Methods

- **M**ulticenter, RCT, blinded end-point evaluation
- **H**igh-dose IV iron sucrose, administered proactively (400 mg monthly, unless ferritin >700 µg per liter or Tsat ≥40%) vs low-dose IV iron sucrose, administered reactively(0 to 400 mg: ferritin <200 µg per liter or Tsat <20% being trigger)
- **P**rimary end point: composite of myocardial infarction, stroke, hospitalization for heart failure, or death
- 2141 regular HD patients randomised; median follow-up 2.1 years

Macdougall et al. N Engl J Med. 2019 Jan 31;380(5):447-458

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Results

- 29.3% in high-dose group had a primary end-point event vs 32.3% in the low-dose group (HR, 0.85; P<0.001 for noninferiority; P = 0.04 for superiority)
- Median monthly ESA dose was 29,757 IU in the high-dose group and 38,805 IU in the low-dose group (median difference, −7539 IU; [CI], −9485 to −5582)
- Less transfusions in High iron dose (-15% pts)
- No difference in vascular access dysfunction / hospitalisation for infection

Macdougall et al. N Engl J Med. 2019 Jan 31;380(5):447-458

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Take-Home Message

High-dose IV iron administered proactively was superior to a low-dose regimen administered reactively and resulted in lower doses of erythropoiesis-stimulating agent being administered

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ESA type and survival

Types of Erythropoietin-Stimulating Agents and Mortality among Patients Undergoing Hemodialysis

Sakaguchi et al. J Am Soc Nephrol. 2019 Jun;30(6):1037-1048

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Sakaguchi et al: Summary

- Nationwide cohort of 194,698 HD patients in Japan
- Receiving either a short-acting (epoetin a/b or epoetin k) or a long-acting (darbepoetin or epoetin b pegol) ESA
- Outcomes: 2-yr all-cause and cause-specific mortality

- Long-acting ESA users had a 13% higher rate of death compared with short-acting ESA users (P<0.001)
- Difference in risk was pronounced among those receiving high doses of ESA (adjusted 2-yr number needed to harm for death was 30.8)

- Conclusion: Among patients undergoing MHD, use of long-acting ESAs might be associated with a higher risk of death than use of short-acting ESAs.

Sakaguchi et al. J Am Soc Nephrol. 2019 Jun;30(6):1037-1048

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METHODS

A nation-wide cohort study in Japan

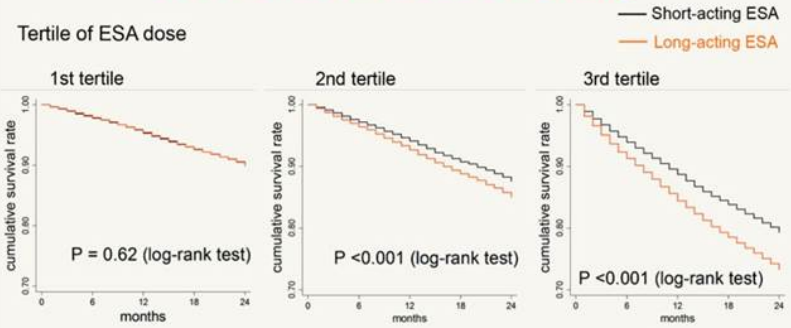
Patients undergoing HD
n=194,698

- 2-year follow-up
- 31,557 deaths occurred

Short-acting ESA	**n=70,631 (36.3%)**
epoetin-alfa/beta	n=50,809 (26.1%)
epoetin-kappa	n=19,822 (10.2%)
Long-acting ESA	**n=124,067 (63.7%)**
darbepoetin-alfa	n=97,391 (50.0%)
epoetin beta pegol	n=26,676 (13.7%)

ESA: erythropoietin-stimulating agents

OUTCOME: All-cause mortality



Multivariable Cox model for all-cause mortality

	adjusted HR	95% CI	P-value
Short-acting ESA	1.00	-	-
Long-acting ESA	1.13	1.10–1.17	<0.001

CONCLUSION

Long-acting ESA use might be associated with a higher rate of death than short-acting ESA use among patients undergoing hemodialysis.

Sakaguchi et al. J Am Soc Nephrol. 2019 Jun;30(6):1037-1048

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Editorial by Drueke et al.

- Study of Sakaguchi contradicts most of existing literature, but the sample size is three- to ten-fold larger than previous studies
- If long-acting ESAs cause greater harm, underlying mechanism for this effect is unprecise
- Findings need to be confirmed—or invalidated—in CKD populations in other geographic regions, ideally in prospective studies with large sample sizes.

Drüecke et al. J Am Soc Nephrol. 2019 Jun;30(6):907-908

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Discussion

- Increasing IV iron dose (400 mg/month): no harm, reduced EPO needs
- Proactive better than reactive
- Short life ESA may be associated with better survival in MHD (or lower doses? 10% vs 25% mortality)

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Dialysis and the elderly

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Nursing home elderly patients and MHD

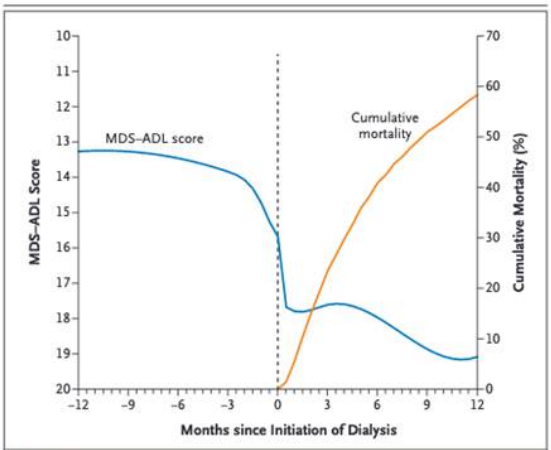

Figure 3. Smoothed Trajectory of Functional Status before and after the Initiation of Dialysis and Cumulative Mortality Rate.
The dashed vertical line indicates the initiation of dialysis in a hypothetical 75-year-old nursing home resident. MDS–ADL denotes Minimum Data Set–Activities of Daily Living. The numbers on the MDS–ADL axis run from highest to lowest.

Kurella Tamura et al. N Engl J Med. 2009 Oct 15;361(16):1539-47

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Dialysis Initiation and Mortality Among Older Veterans With Kidney Failure Treated in Medicare vs the Department of Veterans Affairs

Medicare: > 67 yr, fee-for service
VA: veterans, no financial incentive

100 000 US$ per year at VA

Kurella Tamura et al. JAMA Intern Med. 2018 May 1;178(5):657-664

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Kurella Tamura et al: key points

- Retrospective cohort study of 11215 veterans (98.8% men) with incident kidney failure (eGFR less than 15 mL/min/1.73m^2)
- Patients who received pre-ESRD care in Medicare were more likely to undergo dialysis compared with VA (82% vs 53%)
- Two-year mortality was higher for Medicare compared with VA patients (53% vs 44%)
- Veterans who underwent pre-ESRD care in Medicare receive dialysis more often and were also more likely to die within 2 years compared with those in VA
- Patients with dementia, metastatic cancer or aged >80 y were more frequently started on dialysis through Medicare (80-100%)

Kurella Tamura et al. JAMA Intern Med. 2018 May 1;178(5):657-664

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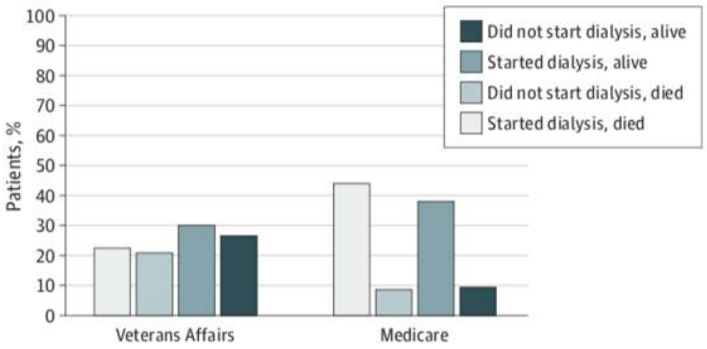
Patients survival Medicare vs VA

Figure 3. Frequency of Death Within 2 Years of Incident Kidney Failure Among Patients Receiving Pre–End Stage Renal Disease Nephrology Care Through Medicare vs Veterans Affairs



Mean age = 80 y

Kurella Tamura et al. JAMA Intern Med. 2018 May 1;178(5):657-664

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Editorial

Dialysis in Older Adults: Is Later Start the Preferred Approach?

Age > 80 y : 78% increase in dialysis start

Box 1. Potential Adverse Quality-of-Life Issues Related to Dialysis Management for Older Adults

- Multiple painful dialysis access surgeries
- Loss of residual kidney function, which has a survival and quality-of-life benefit
- Postdialysis fatigue
- Functional decline after dialysis therapy initiation
- Intradialytic hypotension and cardiac ischemia
- Increased risk for sudden death and stroke
- Much of remaining lifetime spent in the hospital
- Much more likely to die in the hospital vs at home or hospice
- High mortality rate during first 3 months of dialysis therapy

Rosansky et al. Am J Kidney Dis. 2019 Feb;73(2):285-287

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Kidney cachexia or protein energy wasting ?

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Global prevalence of kidney cachexia

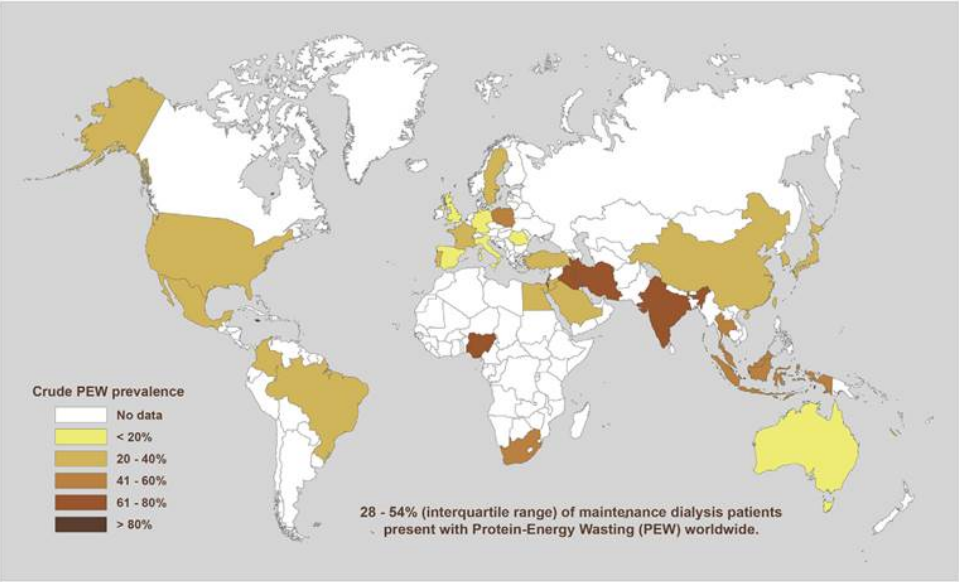

Figure 3. Prevalence of PEW among patients undergoing maintenance dialysis worldwide reported from studies published during 2000-2014. Color gradation reflects PEW prevalence in all included studies from each country (weighted averages within countries). PEW, protein-energy wasting.

Carrero et al. J Ren Nutr. 2018 Nov;28(6):380-392

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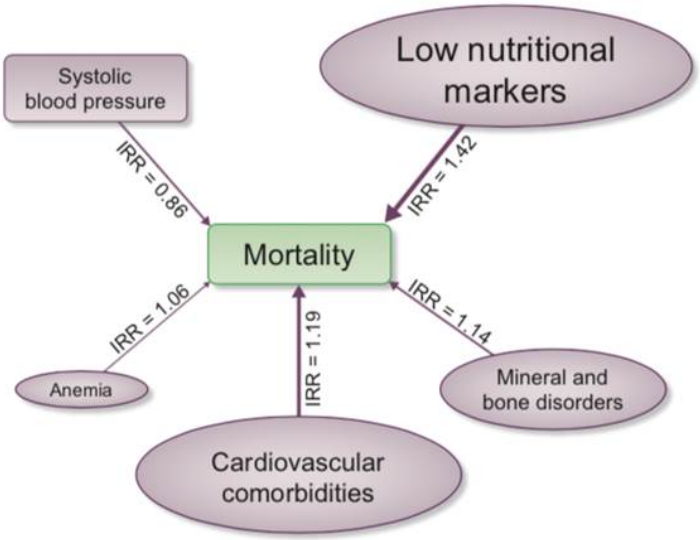
Survival determinants in elderly dialysis patients



- **Prevalent cohort, France**
- **3165 patients > 75 y**

Villain et al. Nephrol Dial Transplant. 2019 May 1;34(5):848-858

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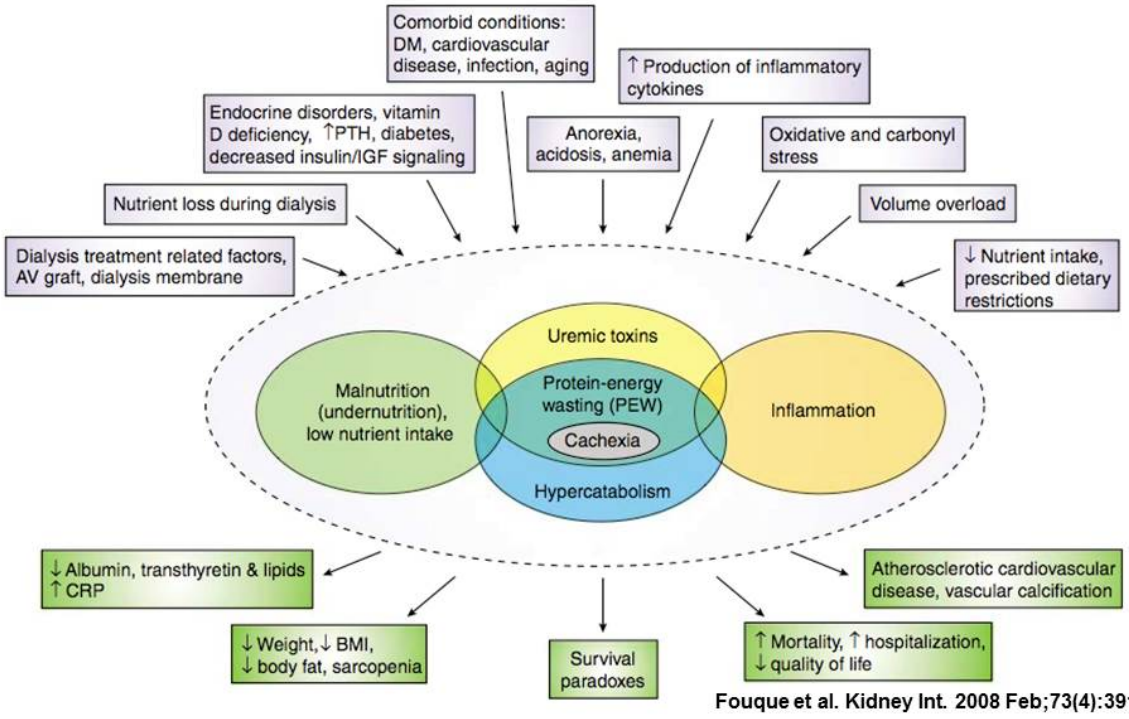
ISRNM - Protein Energy Wasting



Fouque et al. Kidney Int. 2008 Feb;73(4):391-8

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A need for update?

Kidney cachexia or protein-energy wasting in chronic kidney disease: facts and numbers

Koppe et al. J Cachexia Sarcopenia Muscle. 2019 Jun;10(3):479-484

Cachexia/Protein energy wasting syndrome in CKD: Causation and treatment

Oliveira et al. Semin Dial. 2019 Jul 8. doi: 10.1111/sdi.12832

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Diagnosis criteria for PEW/cachexia

Criteria	PEW (ISRNM)	Cachexia (SCWD) *All diseases*
Serum chemistry	Serum albumin <38 g/L Serum prealbumin (transthyretin) <300 mg per 100 mL (for maintenance dialysis patients only) Serum cholesterol <100 mg per 100 mL[a]	Serum albumin <32 g/L Anaemia <12 g/dL Increased inflammatory markers CRP (>5.0 mg/L), IL-6 (>4.0 pg/mL)
Body mass	BMI <23 kg/m^2 Unintentional weight loss over time at least 5% over 3 months or 10% over 6 months Total body fat percentage <10%	BMI <20 kg/m^2 Unintentional weight loss of at least 5% in 12 months
Muscle mass	Muscle wasting: reduced muscle mass 5% over 3 months or 10% over 6 months Reduced mid-arm muscle circumference area (reduction >10% in relation to 50th percentile of reference population) Low creatinine appearance	Reduction of appendicle skeletal muscle index by DEXA (kg/m^2) <5.45 in women and <7.25 in men. Reduced mid-arm muscle circumference area (<10th percentile for age and gender) Fatigue = defined as physical and/or mental weariness resulting from exertion; an inability to continue exercise at the same intensity with a resultant deterioration in performance.
Dietary intake	Unintentional low DPI <0.80 g kg^{-1} day^{-1} for at least 2 months[e] for dialysis patients or <0.6 g kg^{-1} day^{-1} for patients with CKD stages 2–5 Unintentional low DEI <25 kcal kg^{-1} day^{-1} for at least 2 months[e]	Unintentional low DEI <20 kcal kg^{-1} day^{-1} Unintentional DEI <70% of usual food intake Poor appetite
Definition of PEW/ cachexia	At least three out of the four listed categories (and at least one test in each of the selected category)	Weight loss of at least 5% in 12 months or BMI <20 kg/m^2, plus three of the other criteria

Less severe **Inflammation**

- No obvious physiopathologic distinction between PEW and cachexia
- Why limit cachexia to extreme PEW?

Koppe et al. J Cachexia Sarcopenia Muscle. 2019 Jun;10(3):479-484

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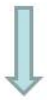
A new definition?

- Protein energy wasting



- Kidney (disease) cachexia

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Guideline in hemodialysis:

Vascular access

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Clinical practice guideline on peri- and postoperative care of arteriovenous fistulas and grafts for haemodialysis in adults

Gallieni et al. Nephrol Dial Transplant. 2019 Jul 19. pii: gfz153

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AV fistulas and AV grafts

- Previous version released in 2007
- 3 yr process – Grade system
- Permanent catheters will be addressed later
- Distinction between maturation and patency
- 32 statements
- 5 strong recommendations (« we recommend »)
- no level A evidence; 4 level B; 28 lower evidence

Gallieni et al. Nephrol Dial Transplant. 2019 Jul 19. pii: gfz153

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Summary

Recommendation number	Type of intervention	Fistula/graft	Strength	Evidence level	Target
Summary	Medical: 13 Surg/Endovasc: 6 Patient role: 2 Cannulation: 9 Surveillance: 2	Fistula: 22 Graft: 7 Both: 3	1: 5 2: 23 –: 4	A: 0 B: 4 C: 16 D: 12	Maturation: 9 Infection: 3 Timing: 7 Stenosis: 2 Patency: 6 Technique: 2 Needle type: 2 Type of intervention: 1

- **First cannulation AVF after 2 weeks not 4 (1B)**
- **First cannulation AVG before 2 weeks (1B)**
- **Perioperative AB prophylaxis for AVG (1C)**

Gallieni et al. Nephrol Dial Transplant. 2019 Jul 19. pii: gfz153

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Conclusion

- Higher and safe IV iron dose
- Proactive better than reactive iron administration
- Short or long life ESA and survival ?
- Double think before starting dialysis in elderly
- Going back to kidney cachexia ?
- Best timing before 1st cannulation of fistula/graft
- Perioperative AB prophylaxis for AV graft (not fistula)

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List of References

1. Macdougall et al. N Engl J Med. 2019 Jan 31;380(5):447-458
2. Sakaguchi et al. J Am Soc Nephrol. 2019 Jun;30(6):1037-1048
3. Drüecke et al. J Am Soc Nephrol. 2019 Jun;30(6):907-908
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