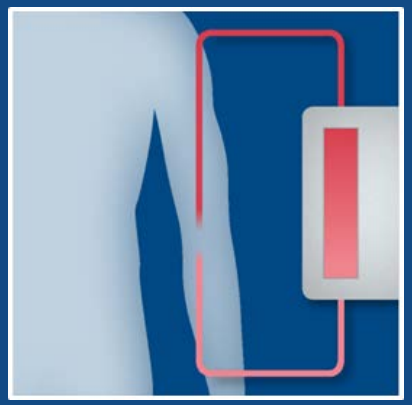
# Nephro Update Europe 2018

## 5-6 October, Budapest

# Hemodialysis



Denis Fouque, France

# Conflicts of Interest

**Research Support: n/a**

**Lecturing: Fresenius Kabi, Amgen, Sanofi, Vifor**

**Consulting activities: Fresenius Kabi, Vifor**

# Antihypertensive treatment

# State of the Art

Blood pressure targets are stil unclear during HD

- Value
- Timing of measure
- Best medication

***Agarwal et al, Nephrol Dial Transplant 2010;25:1766.***
***Bansal et al, Hypertension. 2017;70:435-443.***
***Hannedouche et al Kidney International (2016) 90, 674–684***

# Value

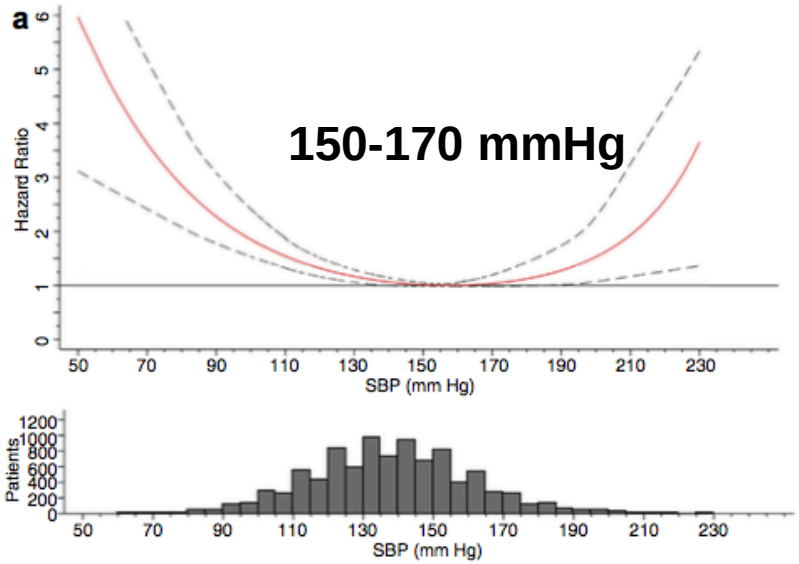
- NKF-KDOQI guidelines (2005): In hemodialysis patients, it is reasonnable to keep BP below 140/90 mmHg

- KDIGO did not want to adress HD in their 2012 BP guideline because of lack of data

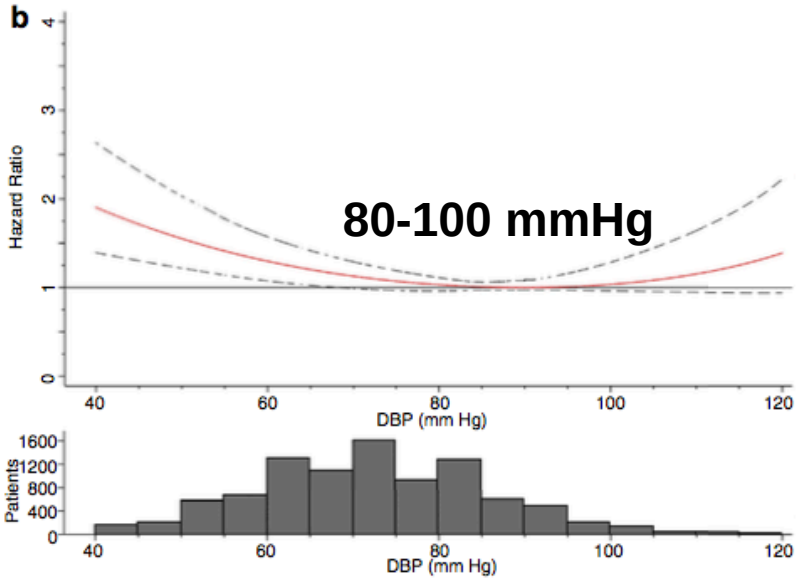
- Consensus papers 2012-2014 with weak evidence

# 2-yr cardiovascular mortality

**SBP**




**DBP**




**9333 prevalent MHD patients**

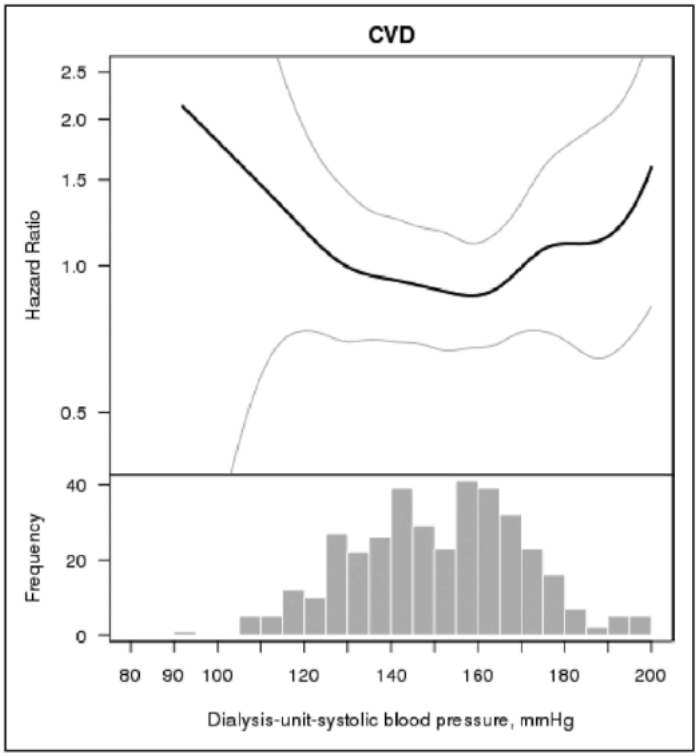
**BP taken predialysis**

*Adjusted fractional polynomials*

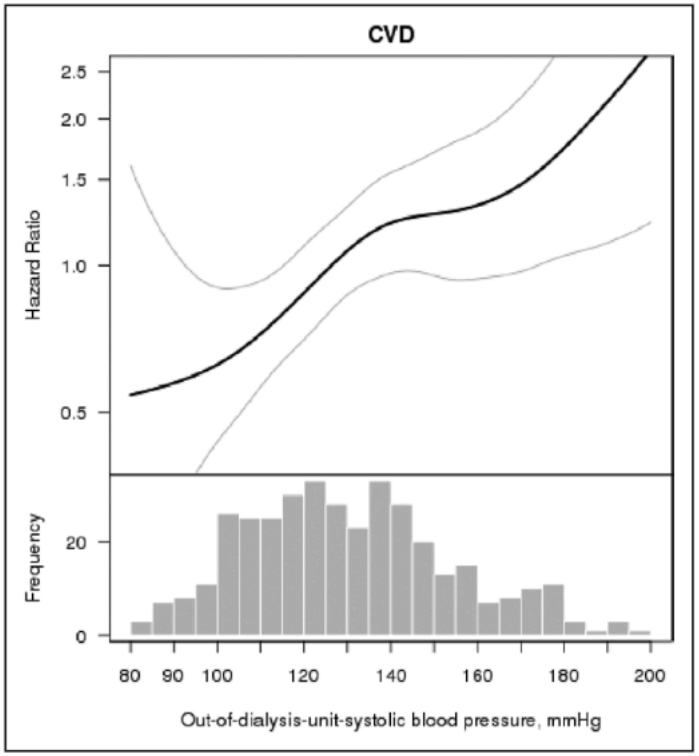
# Timing of measure

# Pre-dialysis vs out of dialysis SBP and CV events

**Per Dialysis**




**Out of Dialysis**




*Mean Follow-up 2.4 yr*

*383 MHD pts, CRIC study USA*



***Bansal et al, Hypertension. 2017;70:435-443.***

# Which BP treatment class in dialysis?

*Original Articles*

## Hypertension in hemodialysis patients treated with atenolol or lisinopril: a randomized controlled trial

Rajiv Agarwal, Arjun D. Sinha, Maria K. Pappas, Terri N. Abraham and Getachew G. Tegegne

Department of Medicine, Indiana University School of Medicine and Richard L. Roudebush Veterans AdministrationMedical Center, Indianapolis, IN, USA

- **RCT**
- **Better BP control and reduction in LVH with atenolol**
- **No survival data**



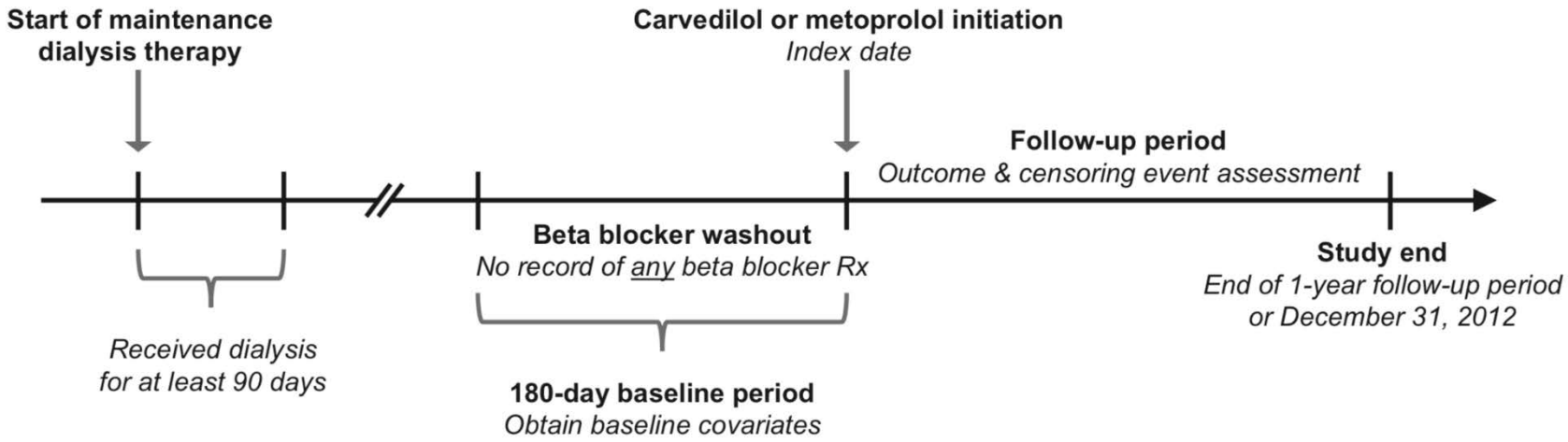
***Nephrol Dial Transplant 2014;29:672-681***

# Which BP treatment in dialysis?

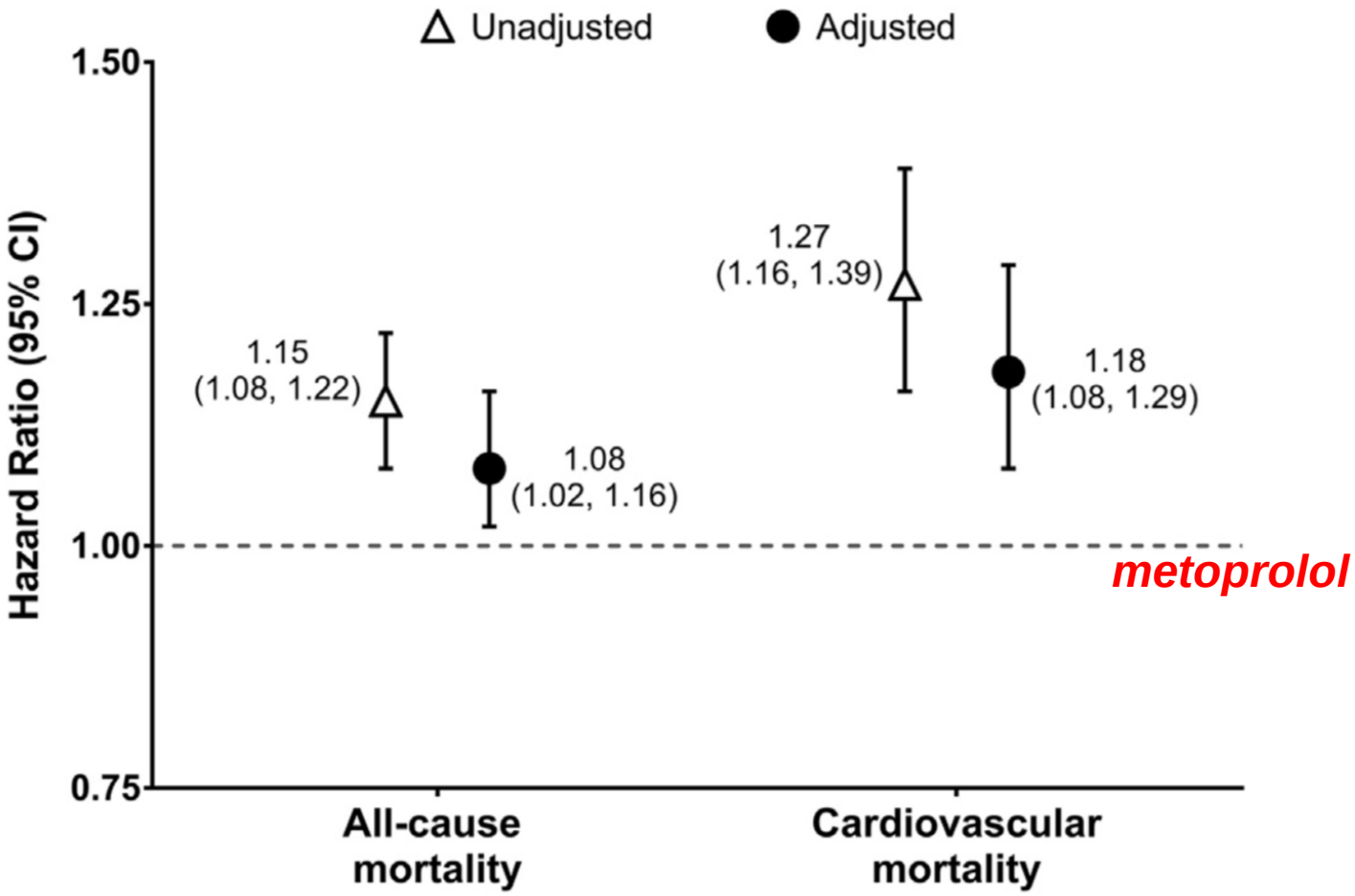
**A Comparative Study of Carvedilol Versus Metoprolol Initiation and 1-Year Mortality Among Individuals Receiving Maintenance Hemodialysis**

- **Carvedilol: non-selective, also α-blocking, poorly dialyzable**
- **Metoprolol: cardio-selective, highly dialyzable**
- **C + M represent 50% of all prescribed beta-blockers in the US**
- **USA, USRDS, retrospective but comparable groups (MI, HF, AF, HTN), propensity scores**
- **Survival and cardiovascular events**


27,064 hemodialysis patients included in the study
9,558 carvedilol initiators
17,506 metoprolol initiators

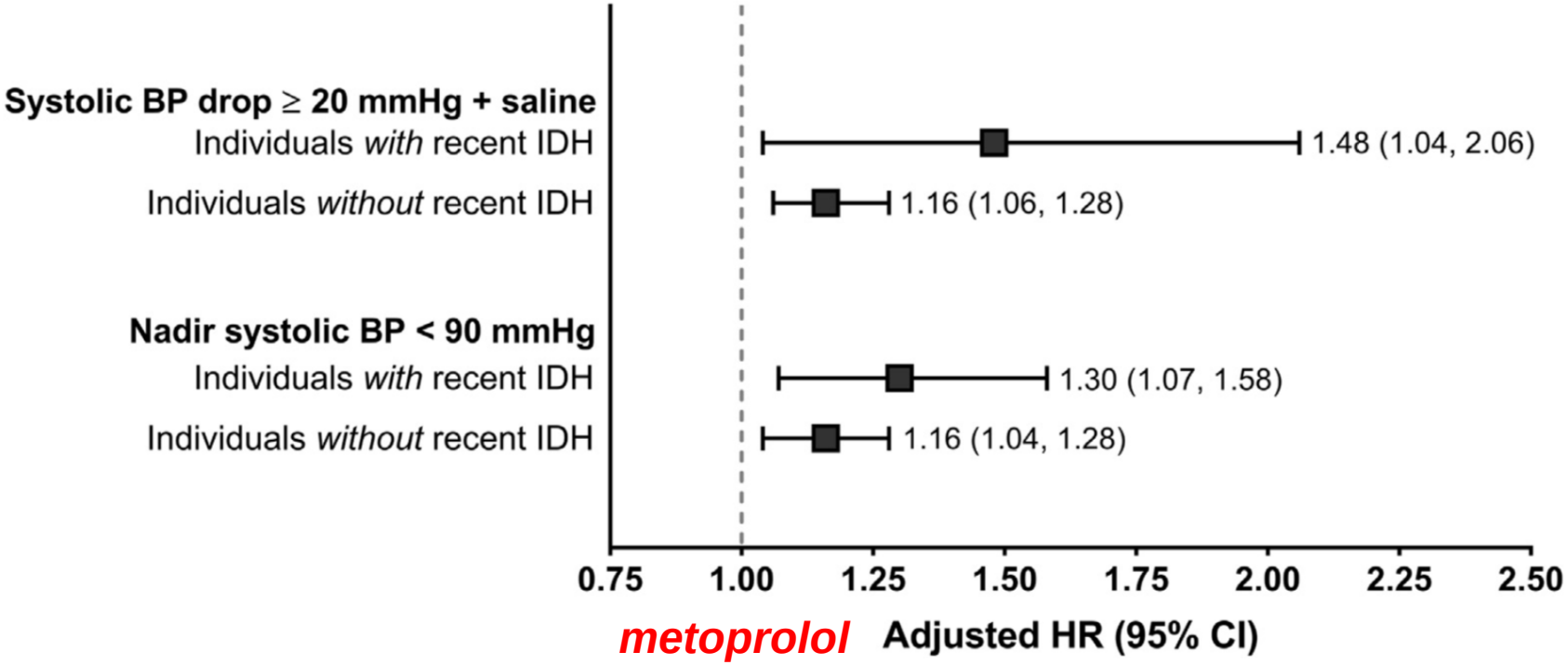

Start of maintenance dialysis therapy
Carvedilol or metoprolol initiation
Index date
Follow-up period
Outcome & censoring event assessment
Beta blocker washout
No record of any beta blocker Rx
Study end
End of 1-year follow-up period or December 31, 2012
Received dialysis for at least 90 days
180-day baseline period
Obtain baseline covariates

# One-yr mortality




Intention to Treat analysis

# Blood pressure patterns



# Interestingly: general population

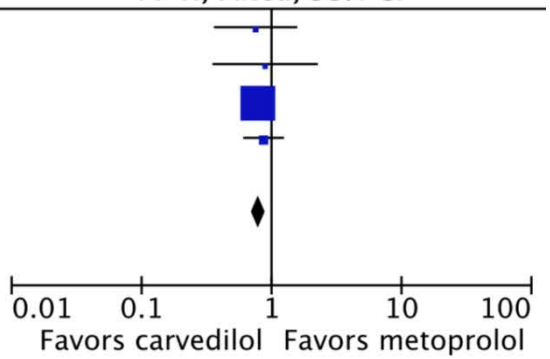


**A**

| Study or Subgroup | Carvedilol Events | Carvedilol Total | Metoprolol Events | Metoprolol Total | Weight | Odds Ratio M-H, Fixed, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Metra et al | 17 | 75 | 21 | 75 | 3.4% | 0.75 [0.36, 1.58] | 2000 |
| Piccirillo et al | 10 | 65 | 11 | 65 | 1.9% | 0.89 [0.35, 2.27] | 2002 |
| COMET | 512 | 1511 | 600 | 1518 | 81.9% | 0.78 [0.68, 0.91] | 2003 |
| MADIT-CRT | 104 | 1077 | 48 | 438 | 12.8% | 0.87 [0.60, 1.25] | 2013 |
| **Total (95% CI)** | | **2728** | | **2096** | **100.0%** | **0.80 [0.70, 0.91]** | |
| Total events | 643 | | 680 | | | | |

Heterogeneity: $Chi^2 = 0.34$, df = 3 (P = 0.95); $I^2 = 0\%$

Test for overall effect: Z = 3.36 (P = 0.0008)




*No difference between carvedilol and metoprolol*

# Summary

- Increased mortality while using carvedilol
- Possibly due to hypotensive status in response to longer half-life

**Limits:**

- Prevalent patients
- Only in center MHD patients, not applicable to Home HD and PD

# Take-Home Message

No valid data to recommend target BP

- Eg diabetes, probably less stringent in-session control in the future
- Best measurement time to be confirmed
- RCTs needed
- B-blockers preferred/ACEi
    - Metoprolol preferred

# HDF and nutrition: the PESET study

# State of the Art

Uncertainty of new convective techniques to improve nutritional status

# New dialysis techniques

Conventional hemodialysis

- Thrice weekly 3-4 h

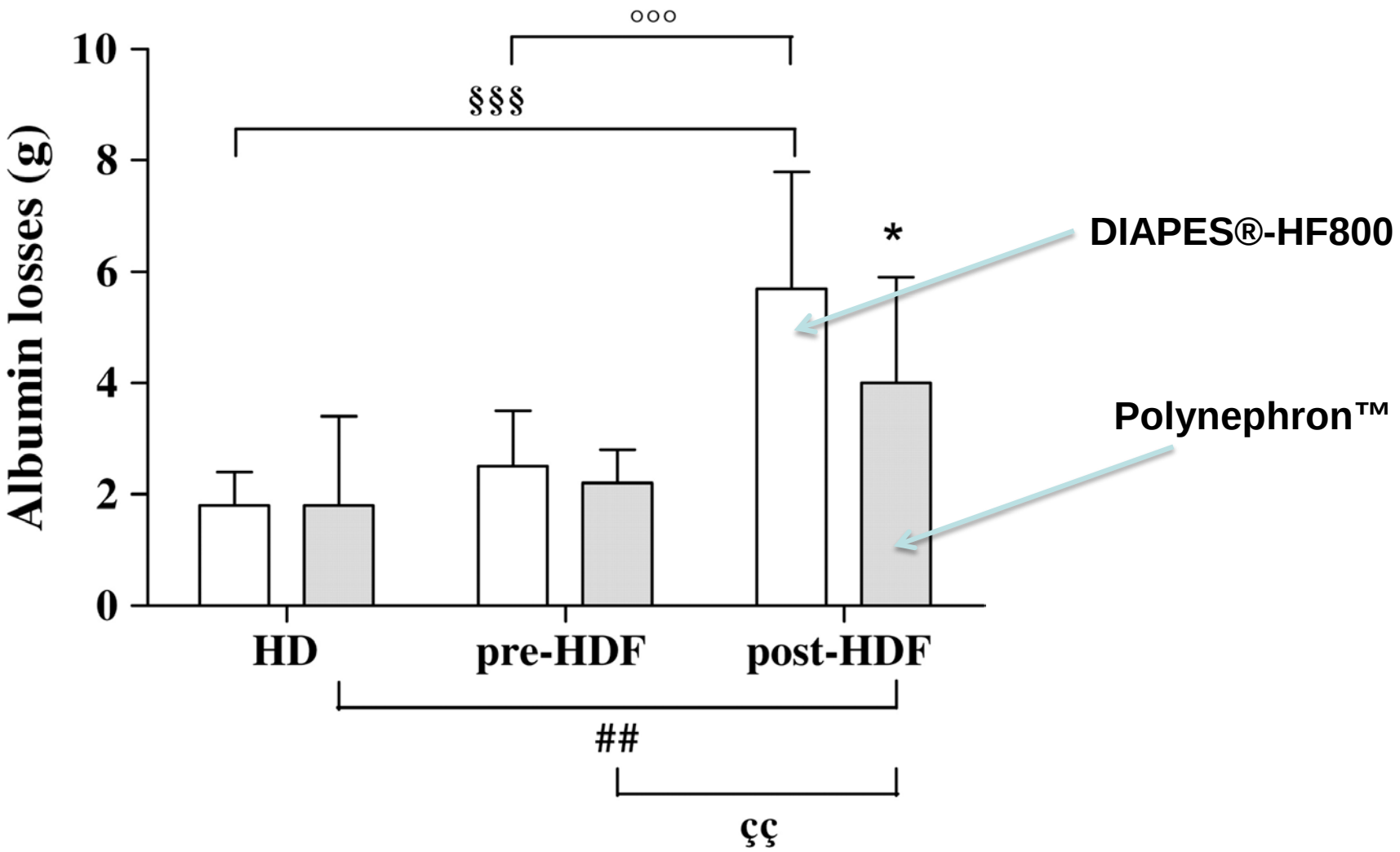
vs:

Intensified hemodialysis

- Hemodiafiltration
- Frequent daily short
- Nocturnal dialysis (3-6; 6 = frequently NHD)

- *not*: incremental dialysis

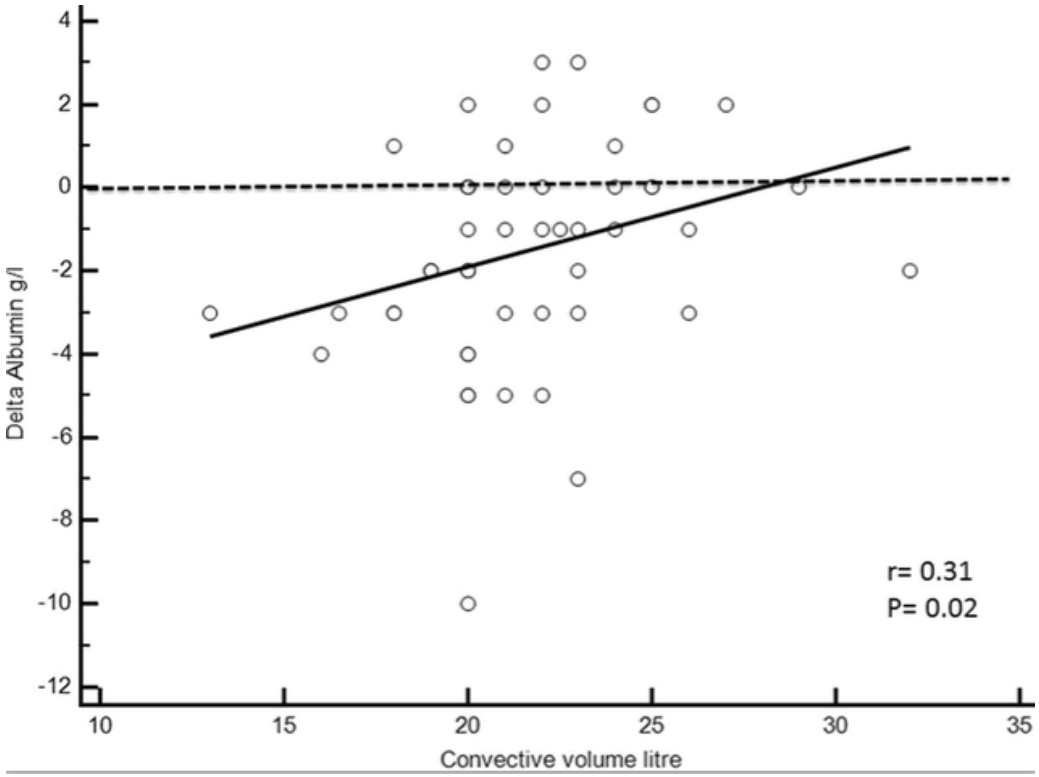
# Albumin losses into dialysate (mean ± SD, n = 14).






*Meert N et al. NDT. 2011;26:2624-2630*

# Albumin variation during HDF according to convection volume




**Before/after non randomized study**



*Jean et al, BMC Nephrol 2015, May 9;16:70*

# Contrast study

## Online hemodiafiltration reduces systemic inflammation compared to low-flux hemodialysis

Claire H. den Hoedt[1,2], Michiel L. Bots[3], Muriel P.C. Grooteman[4,5], Neelke C. van der Weerd[6], Albert H.A. Mazairac[2], E. Lars Penne[4], Renée Levesque[7], Piet M. ter Wee[4,5], Menso J. Nubé[4,5], Peter J. Blankestijn[2] and Marinus A. van den Dorpel[1], for the CONTRAST Investigators[8]

- **RCT**
- **Ultrapure water in both groups**



*DenHoedt et al, Kidney Int 2014, Aug;86(2):423-32*

# Inflammation and convective volume

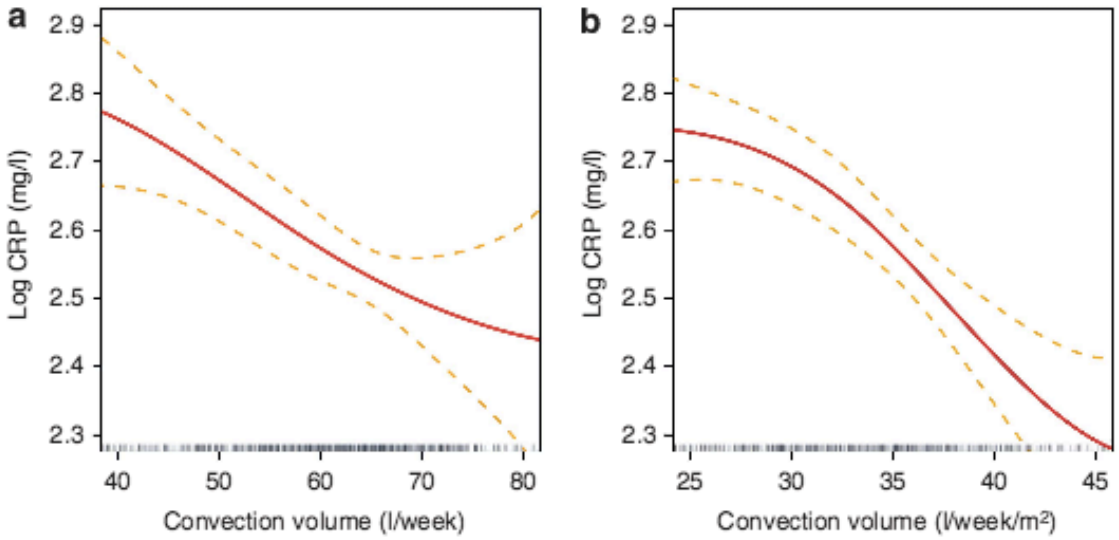



**Figure 8 | Cubic spline analysis of log C-reactive protein concentrations (with 95% confidence interval) versus convection volume adjusted for age, gender, Charlson Comorbidity Index, vascular access, albumin, and Kt/V.** (**a**) l/week. (**b**) l/week/m$^2$ body surface area.

*Kidney International* (2015) **88**, 1108–1116

Nephrol Dial Transplant (2017) 1–12
doi: 10.1093/ndt/gfx342

# The effect of high-volume online haemodiafiltration on nutritional status and body composition: the ProtEin Stores prEservaTion (PESET) study

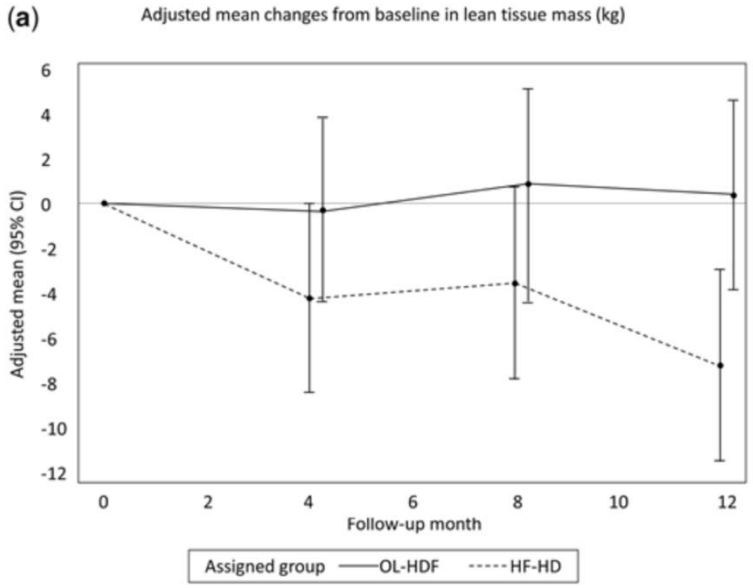
- Pilot RCT, 33 patients, one yr Fup
- High flux HD 3x4.1 hr ultrapure water
- OL HDF 3x4.1 hr ; 23.6 ±3 l/session
- Bioimpedance q4 months

- 60 yr old, BMI 24.5, nPNA 1.17 g/kg, Salb 3.9 g/dl


Molina et al, NDT 2018; 33:1223

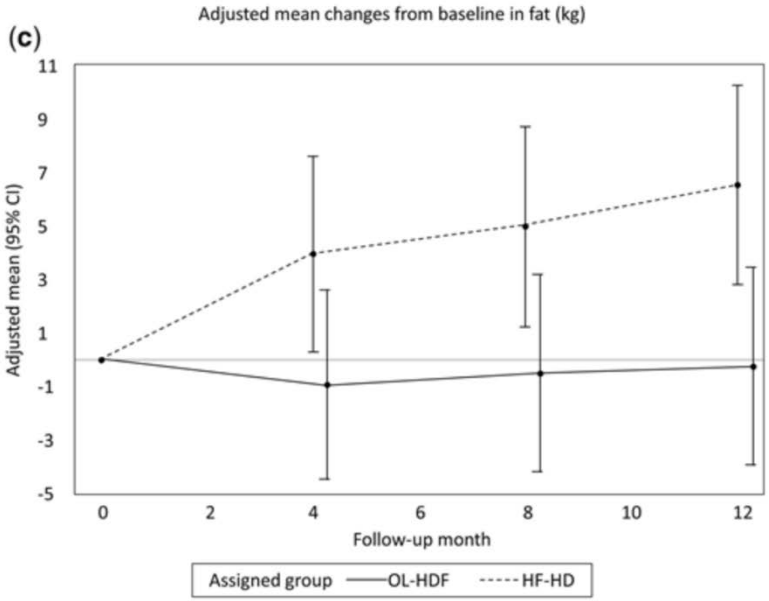
# Body composition change

## LTM




**delta change p<0.05**

## Fat




**delta change p<0.05**

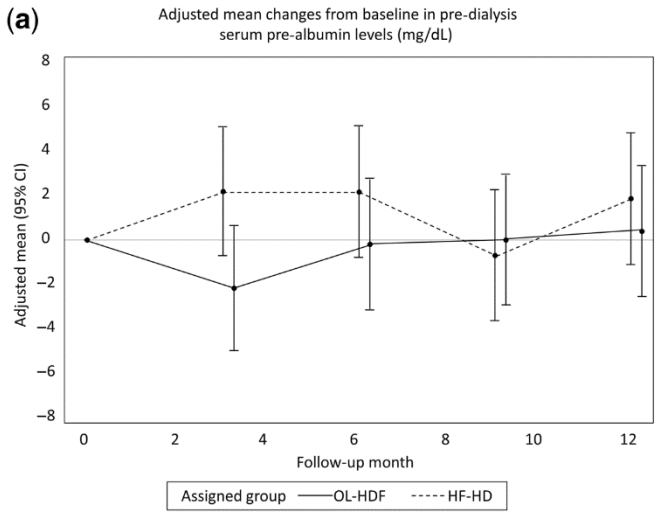


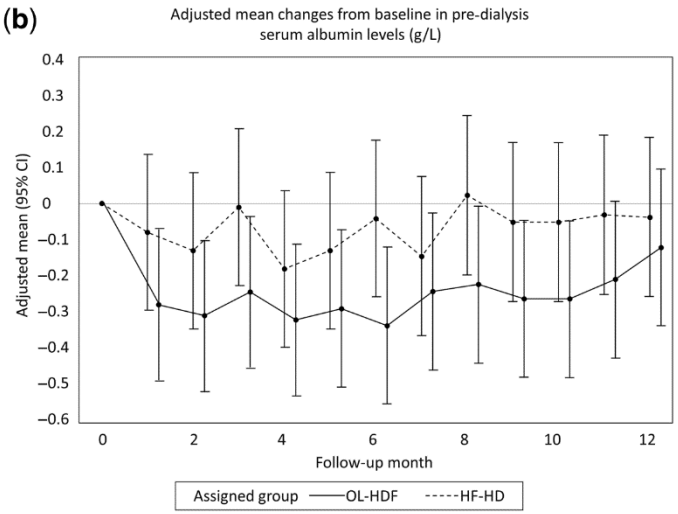
Molina et al, NDT 2018; 33:1223

# Nutritional data

S preAlb

NS

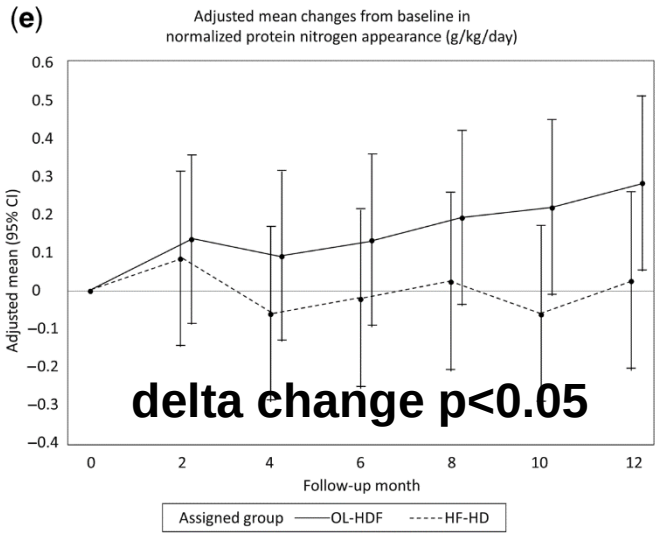


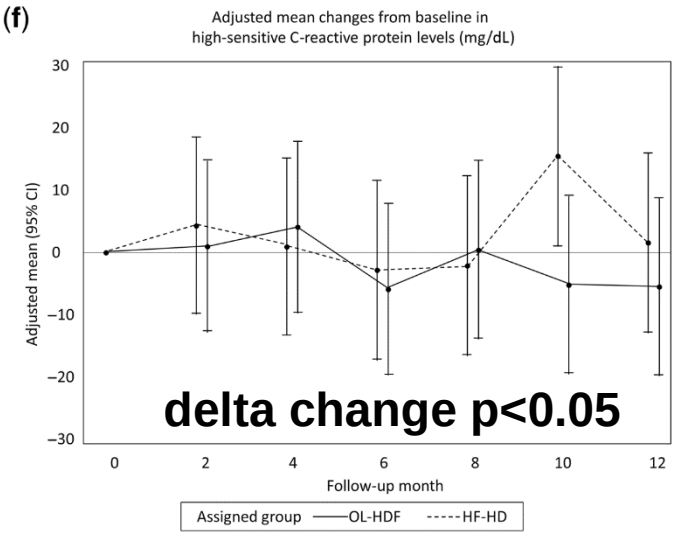




SAlb

NS

nPNA



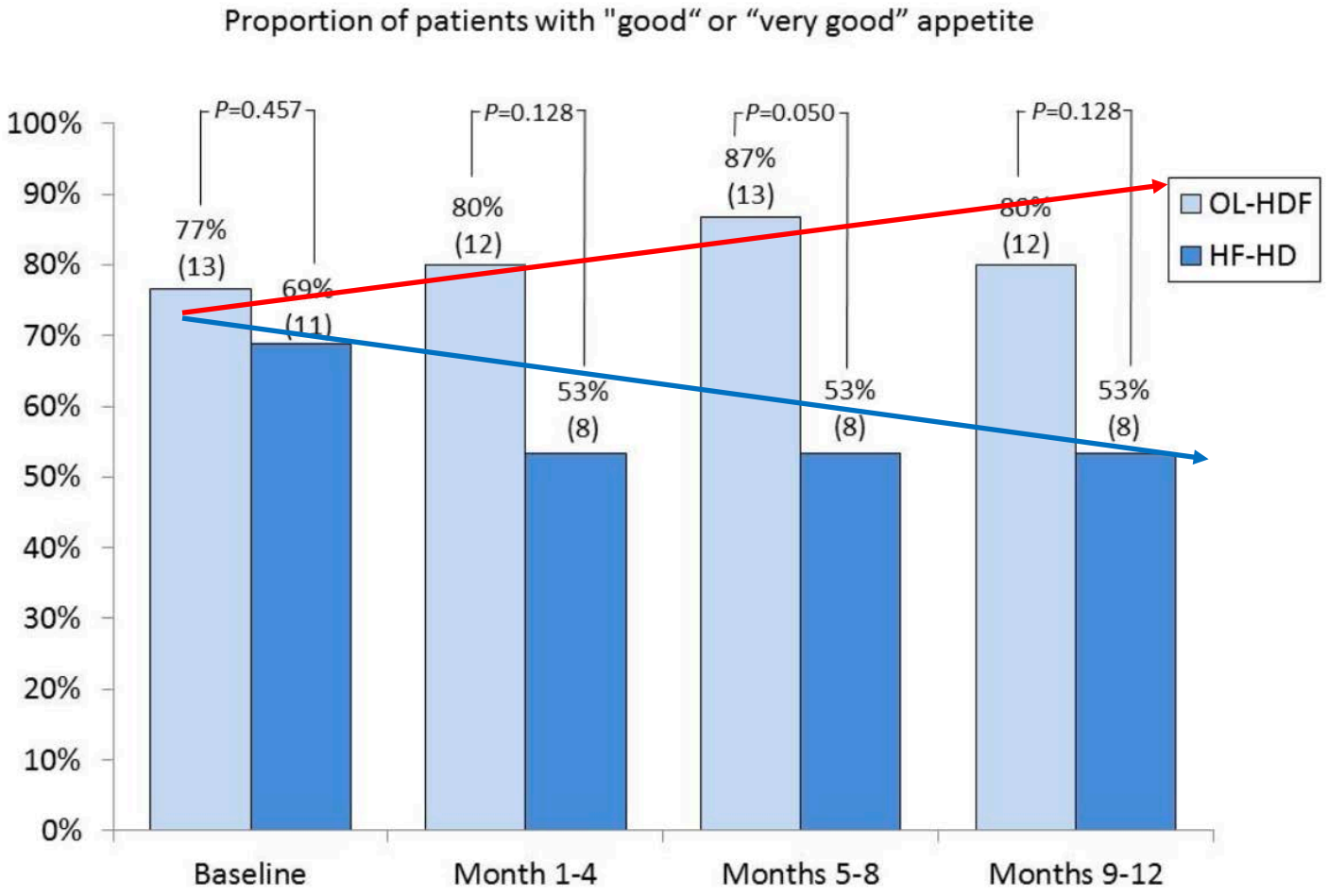




Hs-CrP



Molina et al, NDT 2018; 33:1223

# Appetite






Molina et al, NDT 2018; 33:1223

# Discussion

***vs* HD, 1-yr OL-HDF is associated with:**

- Increase in appetite
- Increase in protein intake
- Stabilization of LTM
- Fat gain control
- Inflammation control

# Summary

- Better understanding of HDF
- Better studies (convective volume > 23 l)
- Better control of inflammation
- Preliminary data on nutritional benefits

- Need for larger RC studies

# Are Proton Pump Inhibitors toxic during maintenance dialyis ?

# State of the Art: Proton pump inhibitors

- 50-80% inappropriately prescribed in geriatrics
- 41% inappropriately prescribed in CKD patients
- 18% inappropriately prescribed in chronic lung disease

**Side effects:**

- Fractures, hypomagnesemia, clostridium difficile
- Kidney disease, CVD and death

- In maintenance dialysis: 25% in Europe, 19% USA

*DeFrancisco et al, Kidney Int Reports 2018;3:374*

# Proton Pump Inhibitor Usage and the Risk of Mortality in Hemodialysis Patients

Angel L.M. de Francisco[1], Javier Varas[2], Rosa Ramos[2], Jose Ignacio Merello[2], Bernard Canaud[3], Stefano Stuard[3], Julio Pascual[4] and Pedro Aljama[5,6,7]; on behalf of the Optimizing Results in Dialysis (ORD) group

- **Retrospective, propensity score, 01/2014 to 09/2016, Spain**
- **2240 MHD patients**
- **Fup 23 months**


Kidney International Reports (2018) 3, 374–384

# Population at inclusion

**79.2% received PPI**

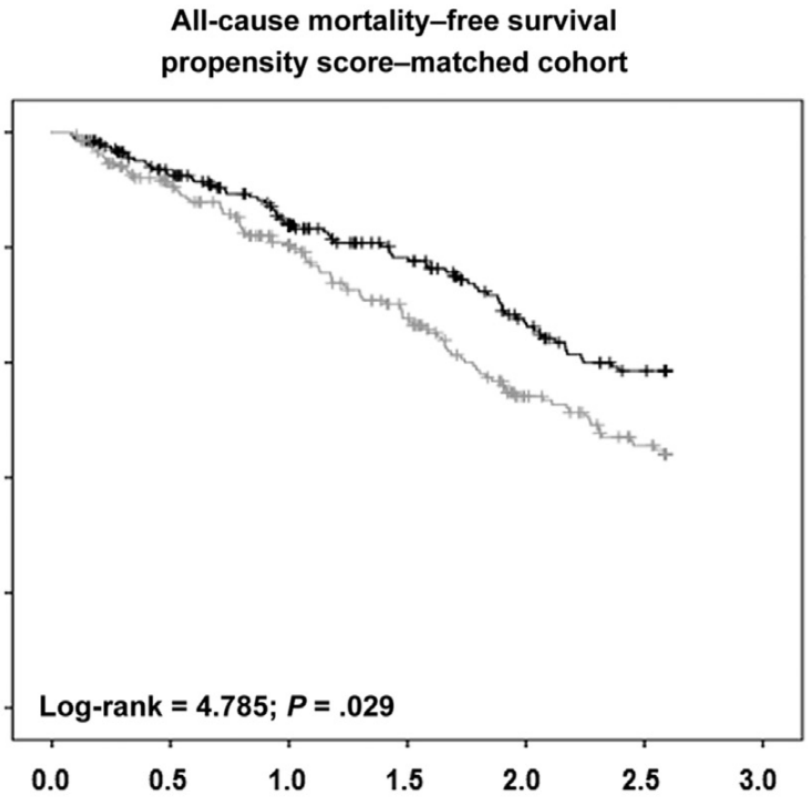
| | No PPI (n = 466) | PPI (n = 1776) | P |
|---|---|---|---|
| Demographics | | | |
| Age, yr | 68.50 (56–76) | 68.00 (57–76) | 0.69 |
| Gender, female | 33.92% | 38.14% | 0.09 |
| Dialysis vintage, mo | 32.19 (16.56–67.96) | 45.60 (21.77–79.15) | <0.01 |
| Diabetes mellitus | 31.94% | 33.06% | 0.65 |
| Charlson Comorbidity Index[a] | 2 (2–3) | 2 (2–3) | 0.24 |
| HD clinical parameters | | | |
| AVF | 74.45% | 69.65% | 0.05 |
| OL-HDF | 53.74% | 44.84% | <0.01 |
| Kt/v | 1.9 ± 0.38 | 1.93 ± 0.4 | 0.17 |
| Td, min | 245.92 ± 11.87 | 246.22 ± 13 | 0.65 |
| SBP pre-HD, mm Hg | 134.91 ± 21.72 | 132.58 ± 23 | 0.04 |
| AvROH | 9.79 (4.23–14.39) | 9.7 (4.26–14.54) | 0.88 |
| Laboratory values | | | |
| Albumin, g/dl | 3.89 ± 0.36 | 3.85 ± 0.36 | 0.03 |
| Hemoglobin, g/dl | 11.71 ± 1.36 | 11.75 ± 1.38 | 0.62 |
| CRP, mg/l | 5.00 (1.80–12.48) | 5.92 (2.00–13.58) | 0.14 |
| Magnesium, mg/dl | 2.41 ± 0.38 | 2.30 ± 0.36 | <0.01 |
| Calcium, mg/dl | 9.02 ± 0.53 | 8.96 ± 0.85 | 0.15 |
| VitD, ng/dl | 15.7 (10.9–24) | 15.5 (10.1–25) | 0.89 |
| Antithrombotic agents | | | |
| Vitamin K antagonists[b] | 7.73% | 11.71% | 0.01 |
| Platelet aggregation inhibitors excluding heparin[c] | 40.13% | 55.07% | <0.01 |
| Systemic corticosteroids | 3.43% | 7.55% | <0.01 |

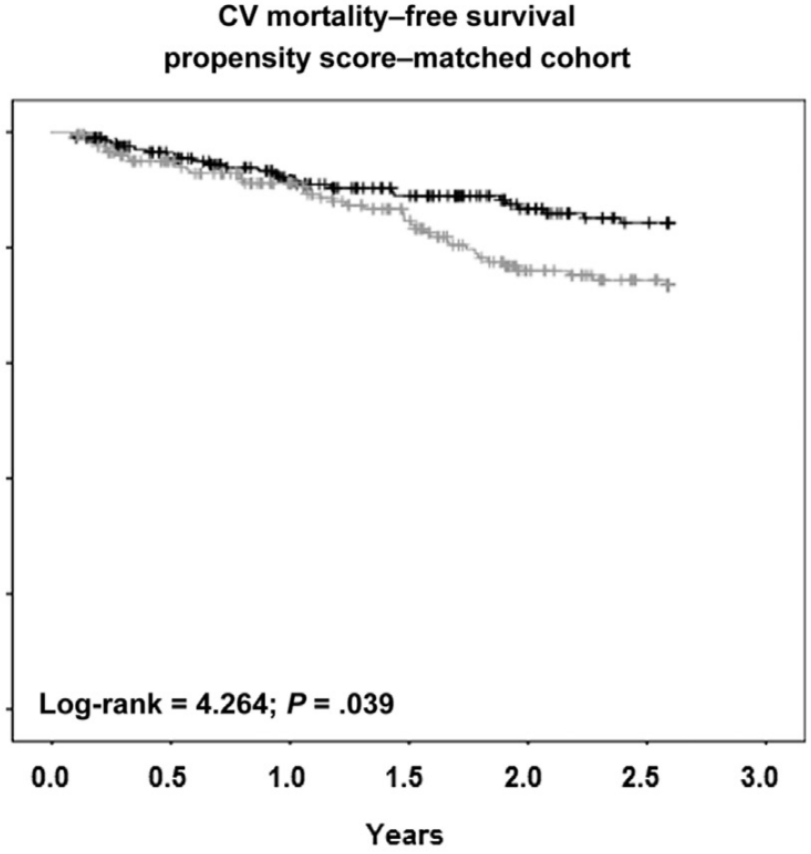
**Necessity for adjustment**

# Determinants of hypomagnesemia (<0.75 mmol/l)

- PPI OR 2.70 p<0.01 multivariate
- HDF OR 1.70 p<0.01 multivariate

# Propensity score survival



# Determinants of mortality

| | | |
|---|---|---|
| • PPI | OR 1.37 | p<0.02 |
| • Diabetes | OR 1.54 | p<0.01 |
| • Catheter | OR 1.29 | p<0.01 |
| • CrP>5 mg | OR 1.85 | p<0.01 |
| • VitK ant | OR 1.50 | p<0.01 |
| • Platelets inhib | OR 1.31 | p<0.01 |
| • Steroids | OR 1.45 | p<0.05 |

Multivariate Cox

# Take-Home Message

**Increased risk of hypomagnesemia and mortality under PPI in MD patients**

- Extremely high prescription in this spanish cohort (79%)
- Many reports of symptomatic hypomagnesemia under PPI
- Unknown mechanism
- Interference with antiplatelet therapy (reduce efficiency)
- Check the dialysate Mg content

# List of References


1. Agarwal et al, Nephrol Dial Transplant 2010;25:1766.
2. Bansal et al, Hypertension. 2017;70:435-443.
3. Hannedouche et al Kidney International (2016) 90, 674–684
4. Assimon et al, Am J Kidney Dis 2018 Aug 30, on-line
5. Briasoulis et al, Am J Cardiol 2015; 115:1111
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7. Jean et al, BMC Nephrol 2015, May 9;16:70
8. DenHoedt et al, Kidney Int 2014, Aug;86(2):423-32
9. Canaud et al. Kidney Int (2015) 88,1108-1116
10. Molina et al, NDT 2018; 33:1223
11. De Francisco et al, Kidney Int Reports 2018;3:374