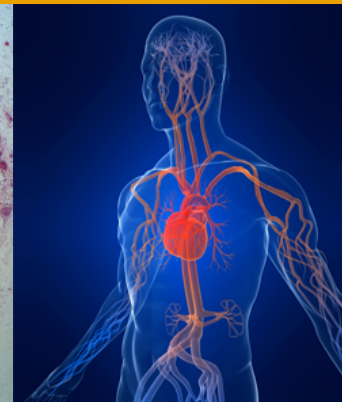
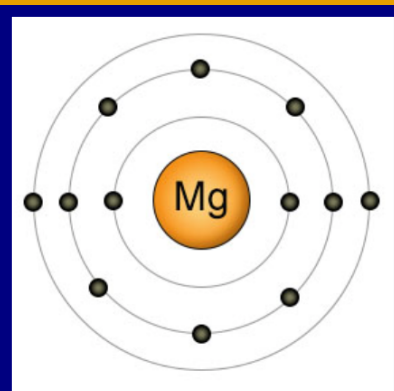


Magnesium in chronic kidney disease

klinische uitkomsten, vaatstijfheid en de MAGIC-HD studie

Niki Leenders
Workshop Nefrologie Papendal
14-12-2022



Disclosure belangen spreker

(potentiële) belangenverstrengeling	Geen



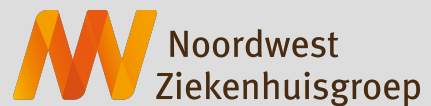
Introduction



Promovendus

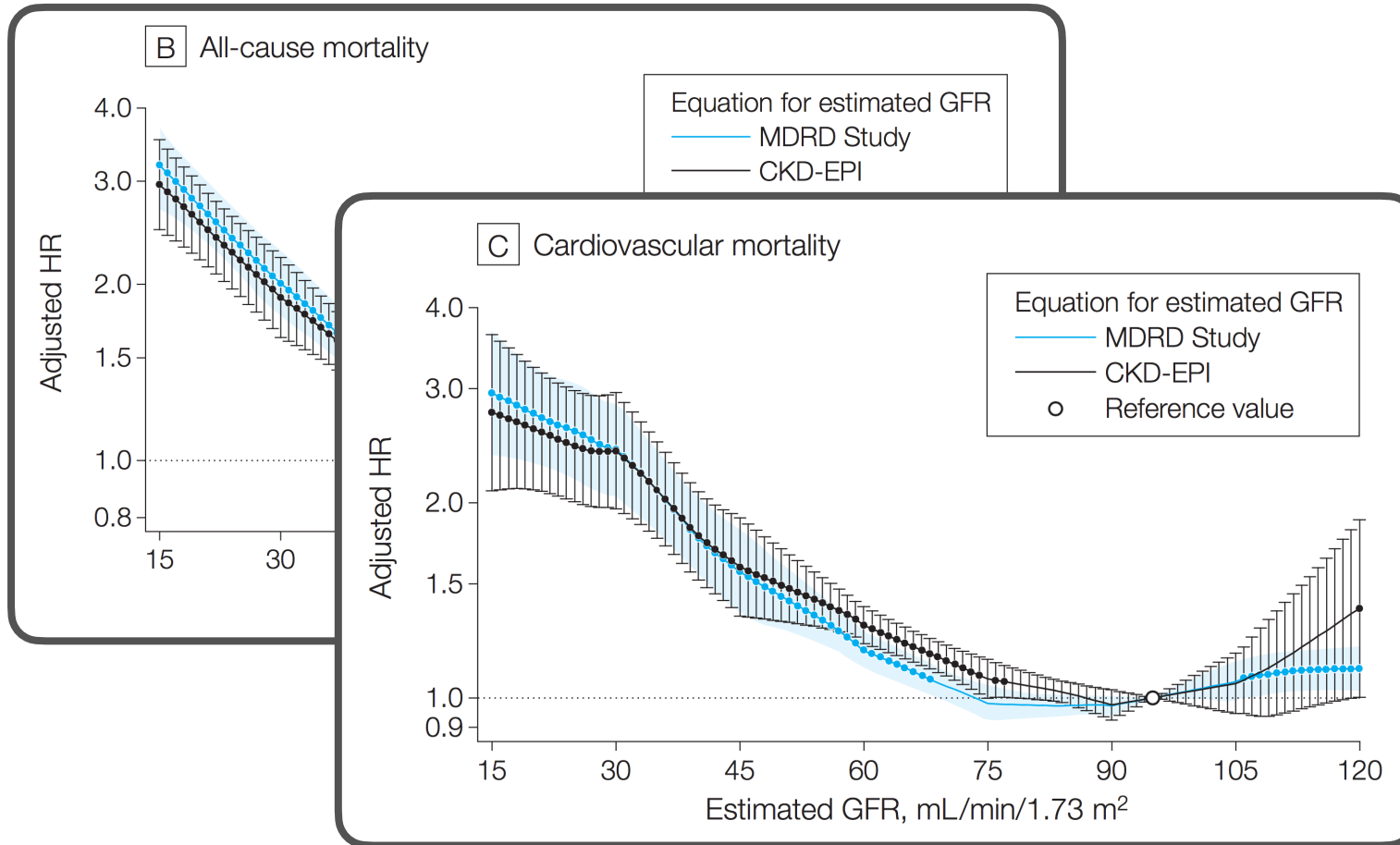


Internist-nefroloog





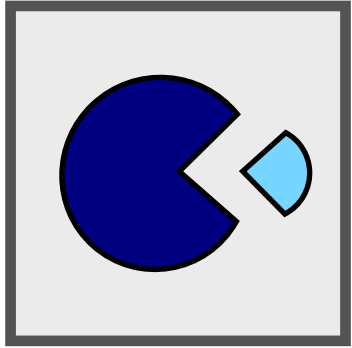
Increased (cardiovascular) mortality in CKD



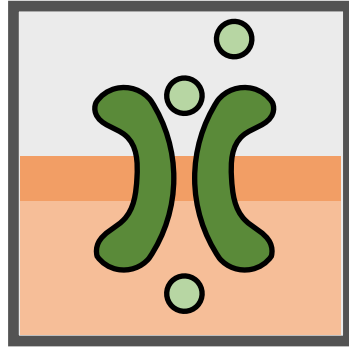
- ▶ Traditional risk factors
- ▶ Kidney specific risk factors
- ▶ Other risk factors?



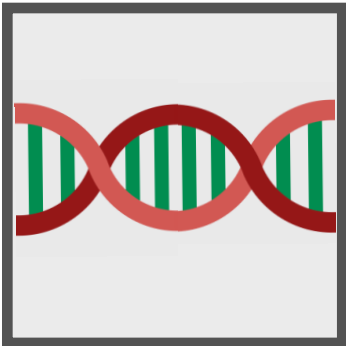
Physiological functions of Magnesium



enzymatic reactions



ion transport



DNA/RNA stability



- ▶ Muscle function
- ▶ Heart rhythm
- ▶ Vascular tone
- ▶ ...



Plasma Mg and mortality in CKD

Meta-analysis

Longitudinal studies with at least 6 months follow-up

P: CKD KDIGO stage I to V-D

I/C: high(normal) vs low(normal) plasma Mg

O: all-cause and cardiovascular mortality

hospitalisation, fractures, progression CKD to RRT

22 studies

348,059 patients

normal vs. low Mg

but also:

high vs. normal Mg

Inverse association of plasma Mg with:

▶ all-cause mortality

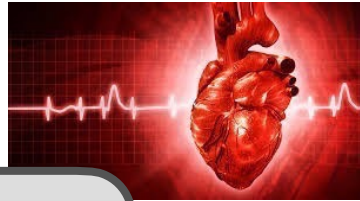
HR 0.90 (0.87-0.94) per 0.1 mmol/L

▶ cardiovascular mortality

HR 0.85 (0.77-0.94) per 0.1 mmol/L



Possible protective mechanisms of Mg



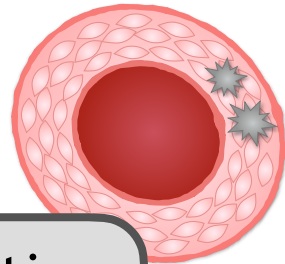
Arrhythmia



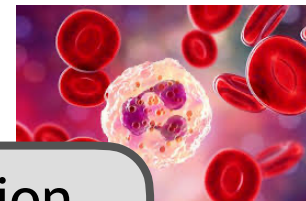
Heart failure



Hypertension



Vascular calcification



Inflammation



Magnesium and arrhythmia

- ▶ Plasma Mg is inversely associated with sudden death^{1,2}

General population

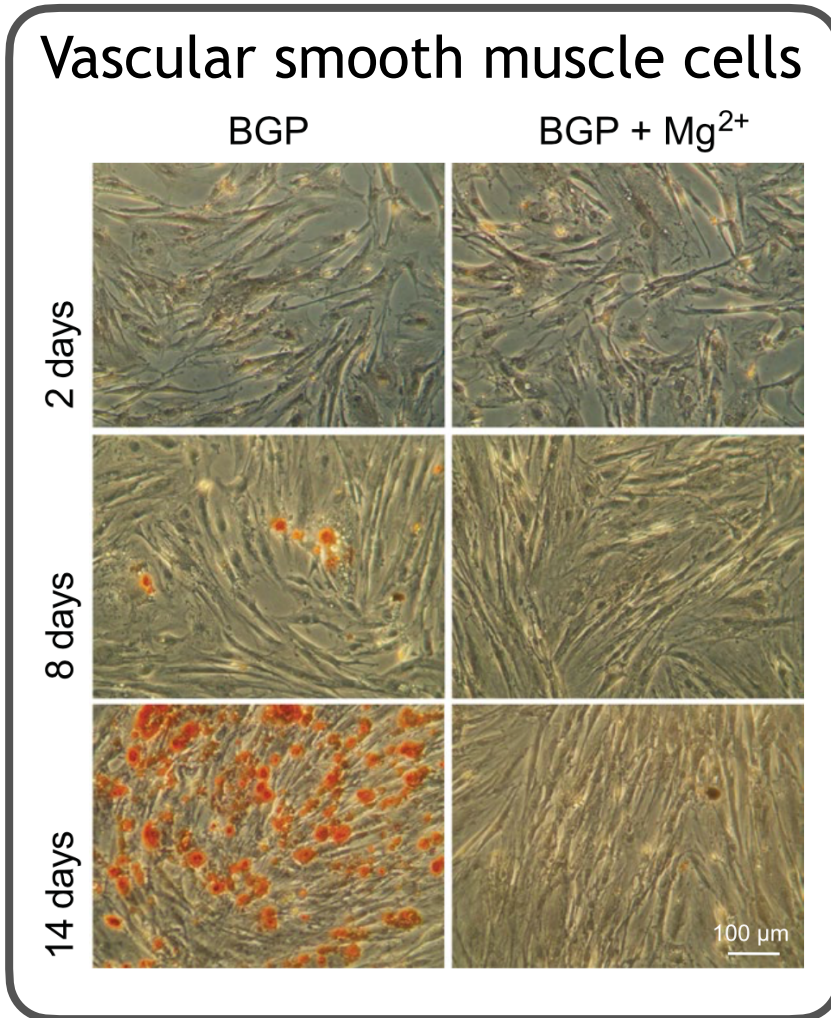
- ▶ Inverse association plasma Mg and complex PVC's³
- ▶ Complex PVC's are associated with mortality⁴

CKD population

- ▶ Inverse association plasma Mg with arrhythmia⁵



Magnesium and vascular calcification

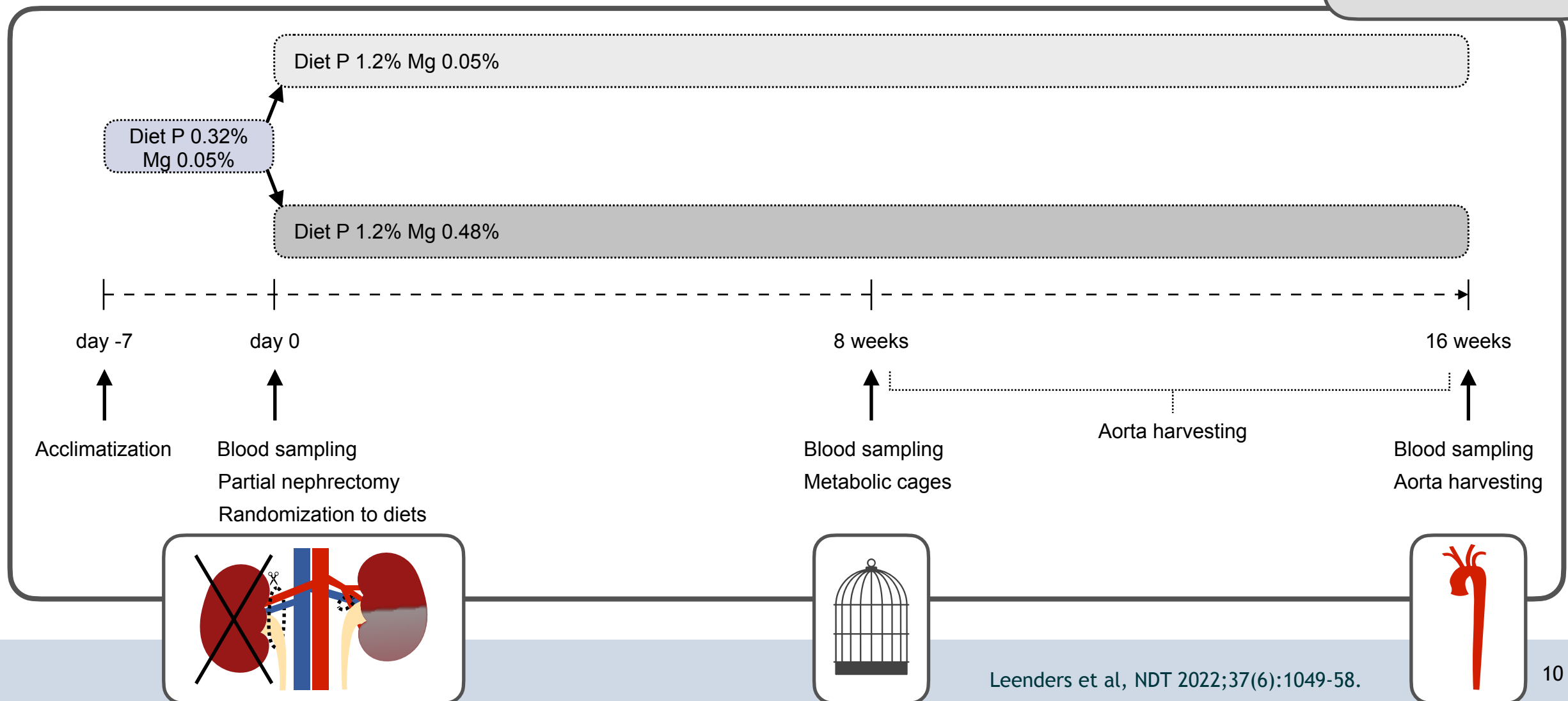




Magnesium and vascular calcification



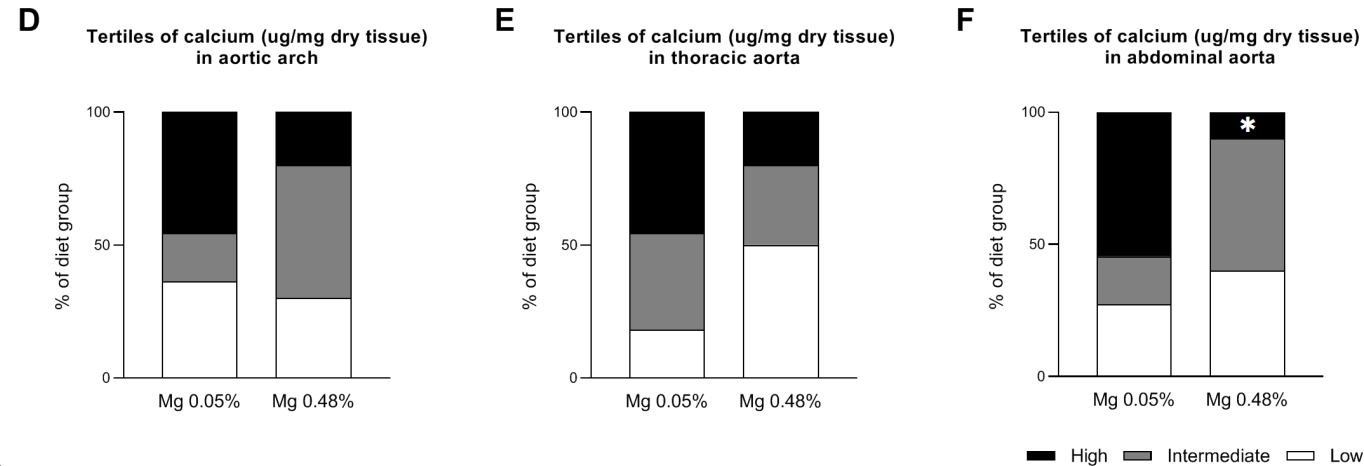
46 Sprague Dawley rats
6-weeks of age





Magnesium and vascular calcification

Rat model of CKD

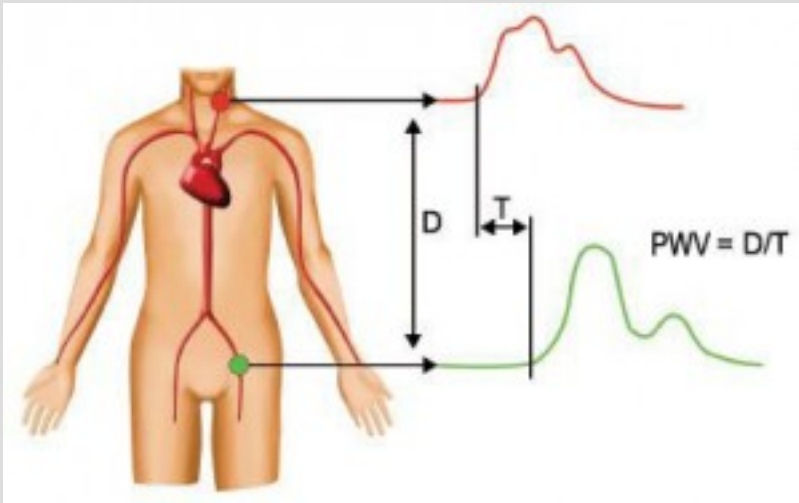


- ▶ High dietary Mg inhibits abdominal aorta calcification in CKD in vivo
 - ▶ Not mediated by phosphate binding actions in the gastrointestinal tract
 - ▶ Dietary Mg was absorbed and available for endogenous effects



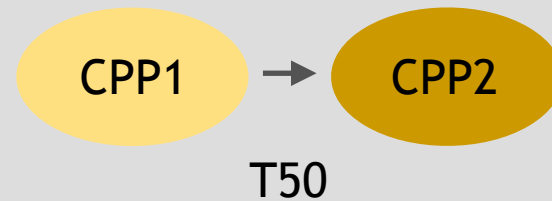
Explorative magnesium-based intervention studies

- ▶ cross-over intervention study¹
- ▶ 30 HD patients
- ▶ 4 weeks dialysate Mg 0.50 -> 0.75
- ▶ improved pulse wave velocity



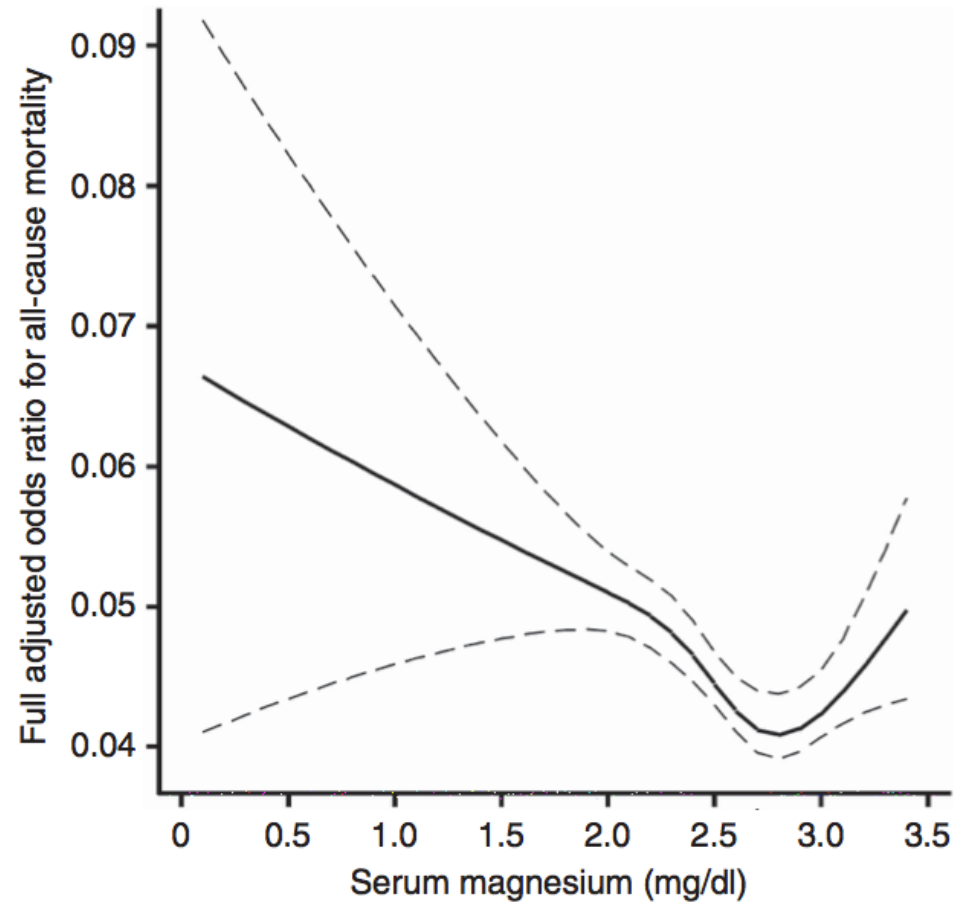
1. Del Gaudio et al, Adv Ther 2020

- ▶ randomized controlled trial²
- ▶ 60 HD patients
- ▶ 4 weeks dialysate Mg 0.50 -> 1.00
- ▶ improved calcification propensity



2. Bressendorf et al, CJASN 2018.

The higher the better?



► plasma Mg 1.27 mmol/L suggested as optimal in hemodialysis



Optimal plasma magnesium level?

0.5-0.70
Neuromusculaire
prikkelbaarheid
Hypocalciemie
Hypokaliemie

1.05-2.1
Asymptotisch

2.9-5.0
Somnolentie
Verlies peesreflexen
Hypotensie
ECG veranderingen

0

1

2

3

4

5

mmol/L

<0.5
Tetanie
Insulten
Arrhythmie

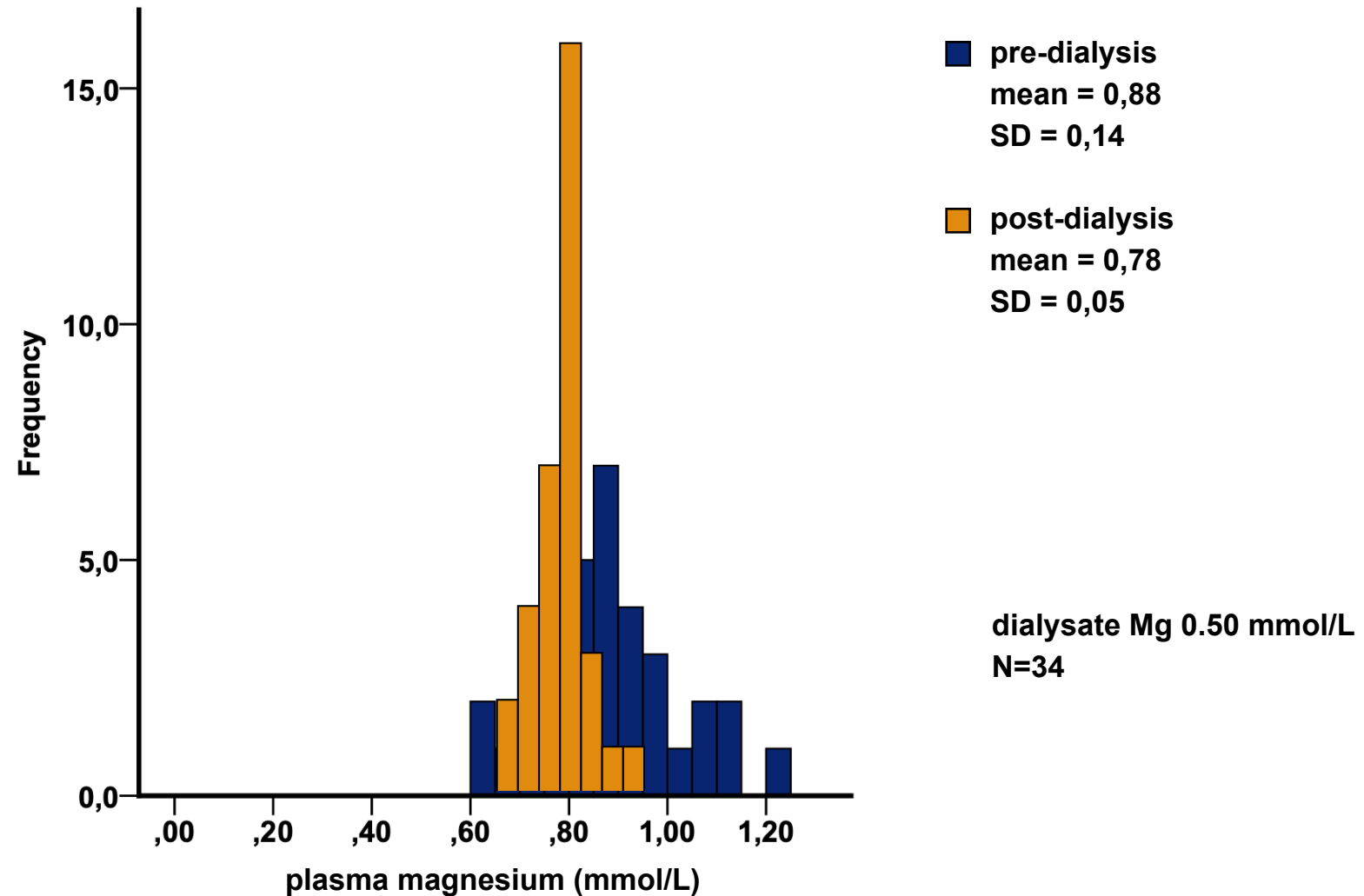
0.70 -1.05
"Normaal"

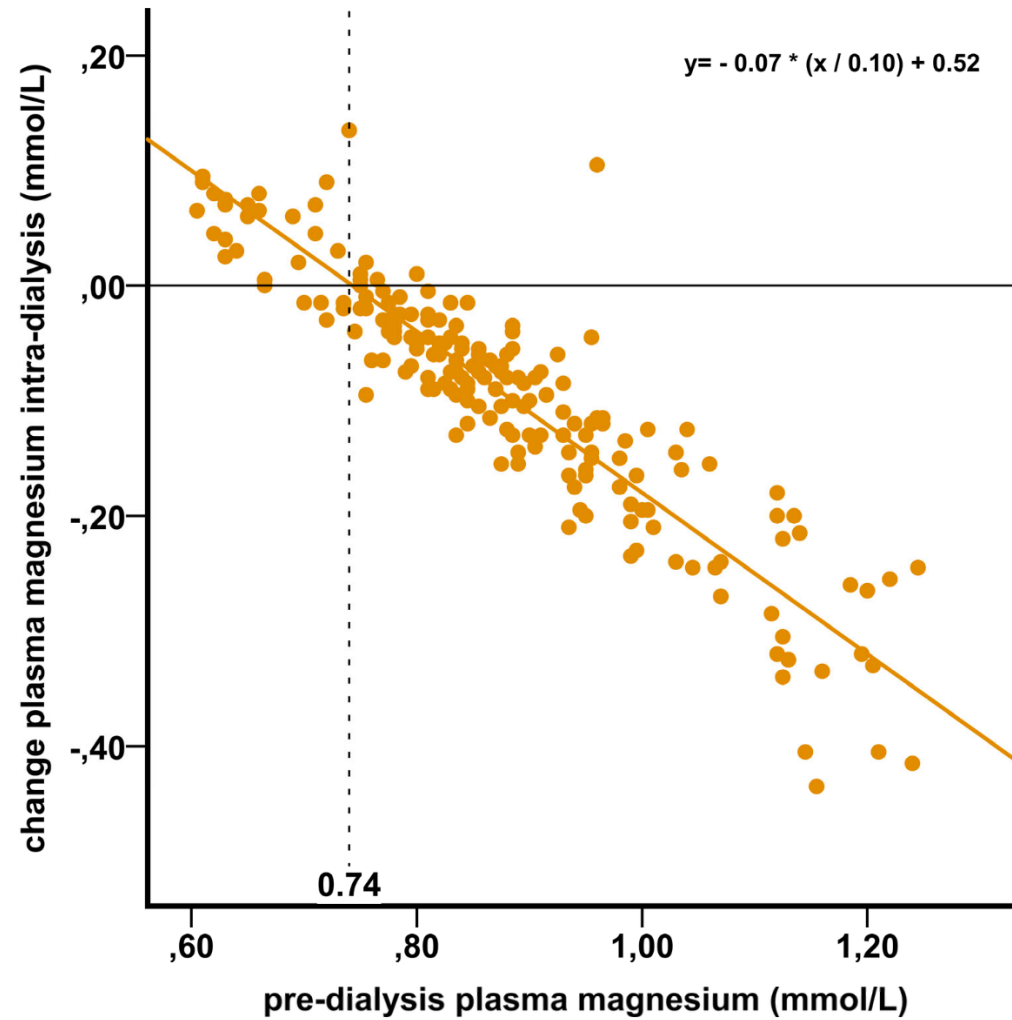
2.1-2.9
Lethargie
Slaperigheid
Flushing
Misselijkheid, Braken
Verminderde peesreflexen

>5.0
Derde graads AV-blok
Hartstilstand
Apneu
Paralyse
Coma



Plasma Mg in hemodialysis





dialysate Mg 0.50 mmol/L
N=34



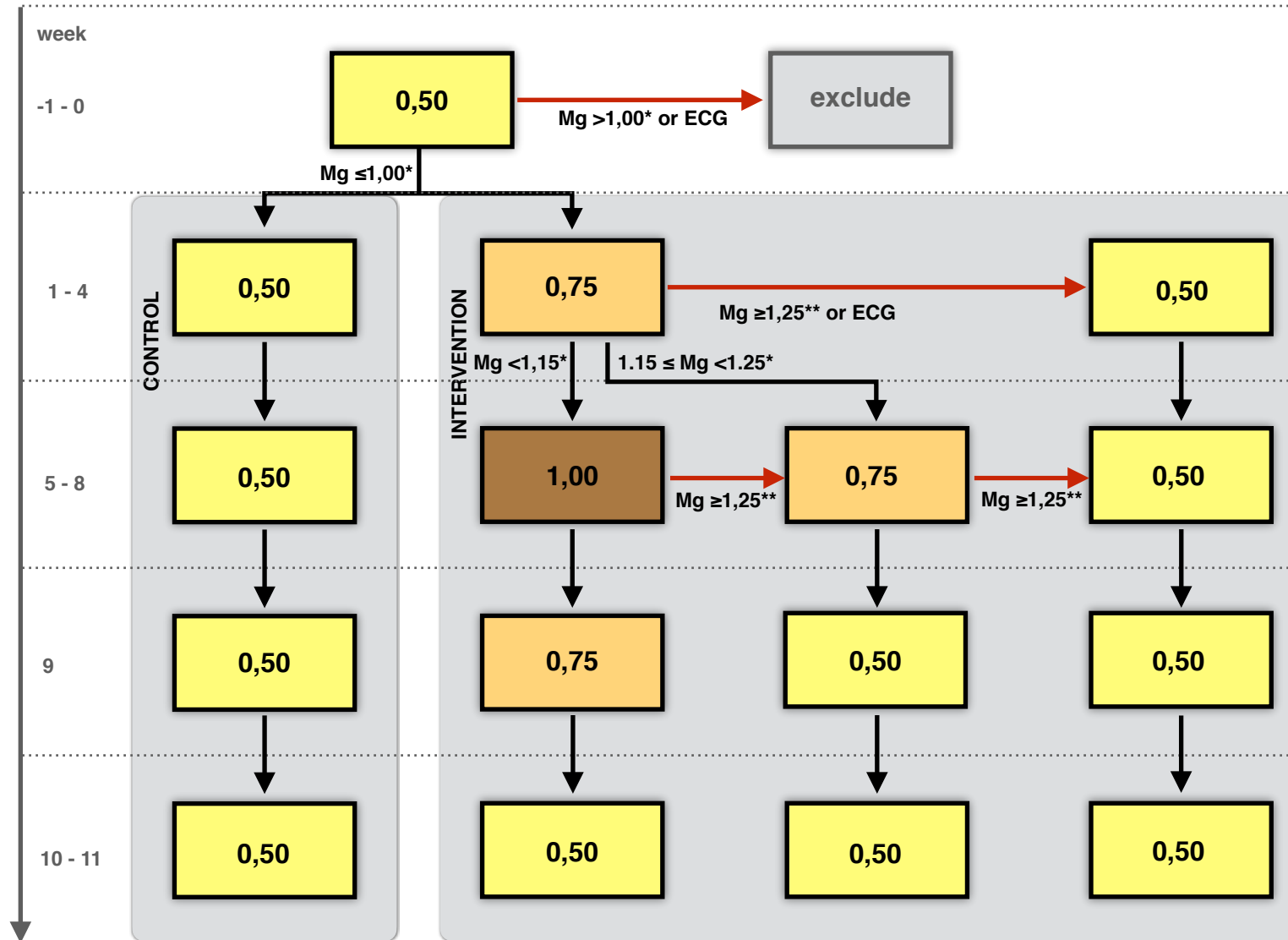
MAGIC-HD study

Magnesium in chronic hemodialysis (MAGIC-HD)

a randomized controlled trial

to determine feasibility and safety of using increased dialysate magnesium concentrations to increase plasma magnesium concentrations in people treated with hemodialysis.

Dialysate Mg





Study procedures

Week	Dialysate	Blood sampling						ECG	Questionnaire	3DDD	Holter	PWV
		dialysis 1		dialysis 2		dialysis 3						
		pre	post	pre	post	pre	post					
-1	standard	set 1	set 1	set 1	set 1			X				
0	standard								X	X	X	X
1	study dialysate	set 3+A+B	set 2	set 1	set 1	set 1	set 1					
2	study dialysate	set 1	set 1									
3	study dialysate	set 1	set 1									
4	study dialysate	set 1	set 1					X	X			
5	study dialysate	set 3	set 2	set 1	set 1	set 1	set 1					
6	study dialysate	set 1	set 1									
7	study dialysate	set 1	set 1									
8	study dialysate	set 1	set 1					X	X		X	X
9	study dialysate	set 3+A	set 2									
10	standard	set 1	set 1									
11	standard	set 1	set 1									



Outcome parameters

- ▶ Pre-dialysis plasma Mg after the long interdialytic interval at the end of week 8
- ▶ Predictive effect of dialysate Mg, other baseline parameters and dialysis characteristics on plasma Mg
- ▶ Safety endpoint: plasma Mg > 1.25 mmol/L, bradycardia, prolonged QTc
- ▶ Explorative endpoints:
 - ▶ change of PWV from baseline to week 8
 - ▶ complex PVC's, PAC's, heart rate variability detected with Holter ECG



Randomisation / Centers

▶ AmsterdamUMC locatie VUMC	▶ 12
▶ Diapriya Buitenveldert	▶ 16
▶ Niercentrum aan de Amstel	▶ 13
▶ Spaarne Gasthuis	▶ 6
▶ Total	▶ 47



Conclusions / Future perspectives

- ▶ Inverse association plasma Mg with (cardiovascular) mortality in CKD
- ▶ Mg has beneficial cardiovascular effects in experimental settings and clinical explorative studies
- ▶ Current plasma Mg in CKD may be too low
- ▶ Increasing plasma Mg in CKD may decrease cardiovascular disease
- ▶ MAGIC-HD: develop strategies to safely increase plasma Mg and identify patients that will benefit from an individualized dialysate
- ▶ Long term randomized controlled trials are needed to determine the effects on clinical outcomes

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