Proton pump inhibition for secondary hemochromatosis in hereditary anemia: a phase III placebo-controlled randomized cross-over clinical trial.

PPI Shine Again Trial

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Funded by ZonMW GGG

SCORE Sickle Cell Outcome Research

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Conflicts of interest and disclaimer

Advisory board: Agios

Research support: Novartis, Bayer, Agios, Pfizer, Mechatronics, ZonMW, H-2020, H-Europe, Eurostars, NHLBI.

Roles:

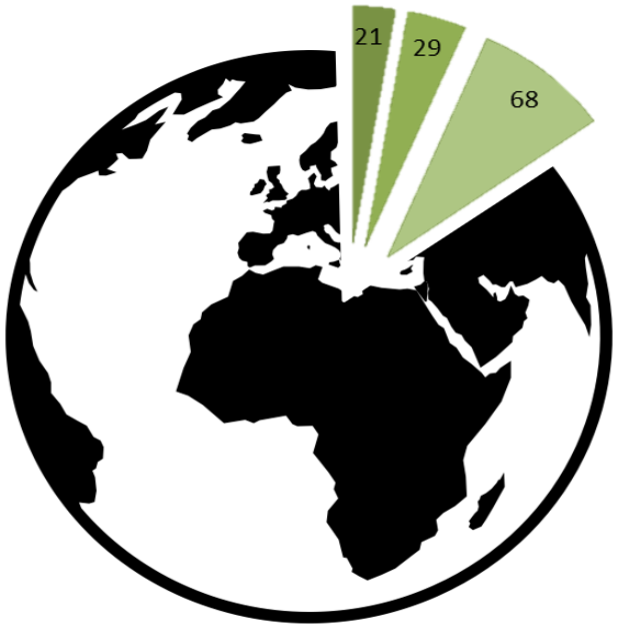
Associate professor hematology, Van Creveldkliniek UMCU

Co-ordinator research and trials benign hematology Eurobloodnet

Clinical trial and innovation lead U-TRIAL, UMCU

Chairman Sickle Cell Outcome Research (SCORE) group, the Netherlands

Global burden of disease: Years lived with anemia

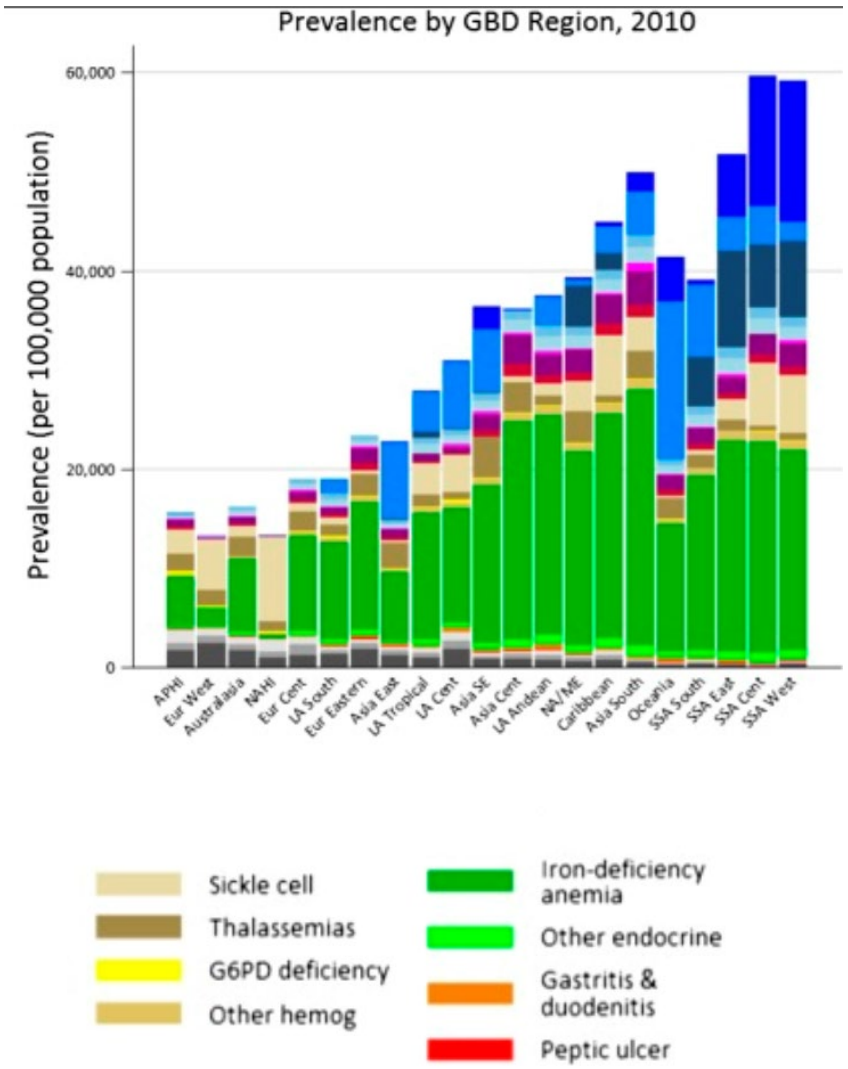


2010

6,916,000,000

772,000,000

dm	21,000,000
copd	29,000,000
anemia	68,000,000



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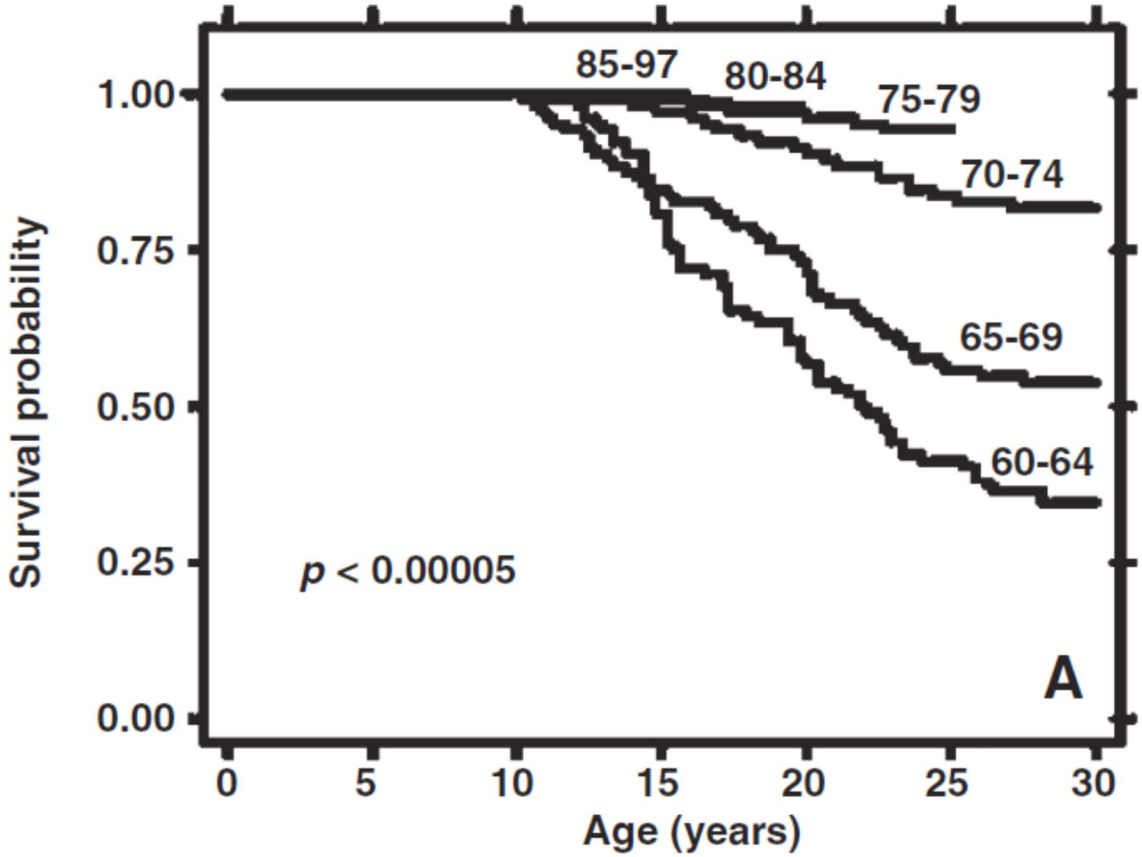
Kassebaum NJ, Blood 2014 Jan 30;123(5):615-624.
GBD group; Lancet Dec 13, 2012

Iron overload and mortality in rare anemia



Iron chelation:

- Incorporated in all guidelines.
- No alternatives
- Treatment-related toxicity
- Very expensive:
  - 10k € pp
  - NL 2019: 7.1 million €

Borgna Pignatti et al. Haematologica 2004

Doel en design van de studie

To show that PPIs compared to placebo are an effective treatment of secondary hemochromatosis in a relative large number of patients with hereditary anemia and mild iron overload.

Intervention

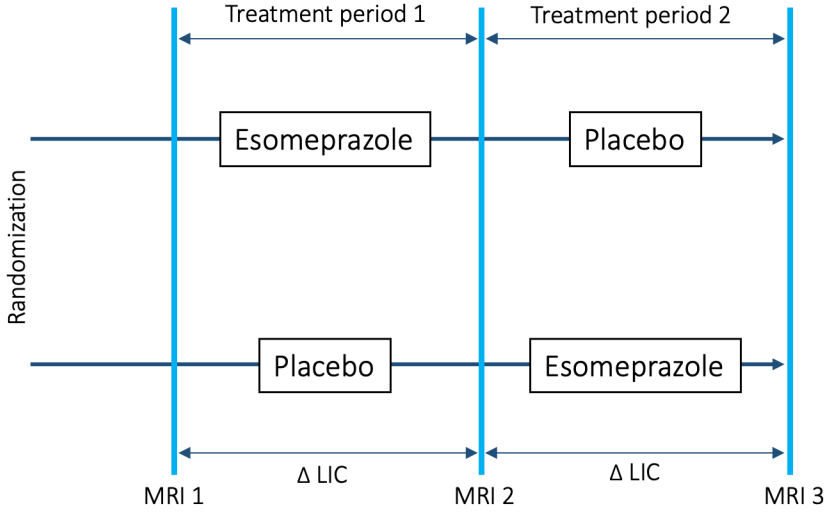
Esomeprazole 2dd40mg vs placebo

Duration per arm: 12 months.

Main Outcome and Measure

Change of liver iron content (MRI).

Other outcomes: safety, QoL, cost-effect.



Results

American Journal of Hematology AJH

RESEARCH ARTICLE | Open Access

Proton pump inhibition for secondary hemochromatosis in hereditary anemia: a phase III placebo-controlled randomized cross-over clinical trial

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Design Phase III randomized placebo-controlled cross-over trial.

Setting Enrollment from March 2018 through April 2019 in five centers of expertise in the Netherlands.

Participants 30 adult patients with mild-to-moderate iron overload were enrolled (non-transfusion-dependent thalassemia (N=13), pyruvate kinase deficiency (N=8), congenital sideroblastic anemia (N=3), congenital dyserythropoietic anemia (N=3), sickle cell disease (N=2), and hereditary elliptocytosis (N=1)).

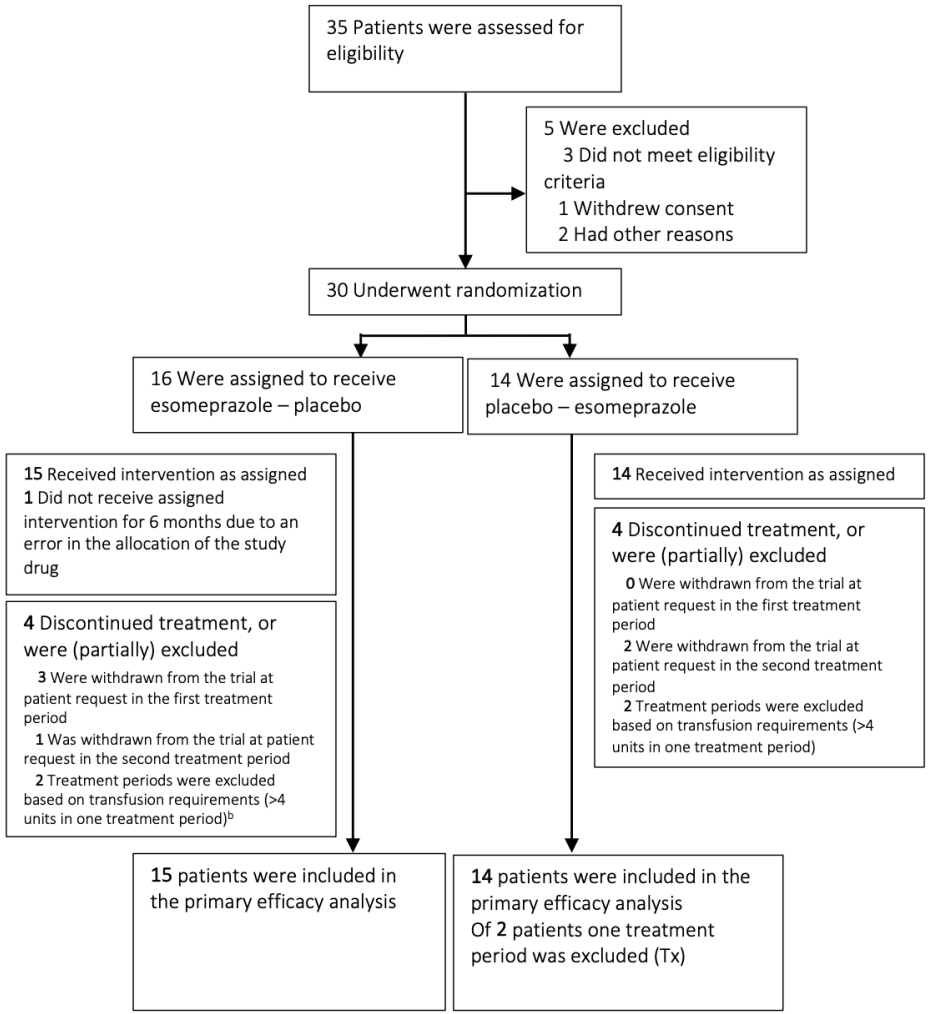

Figure 1.

- 4 treatment periods were excluded based on transfusion requirements (>4 units in 1 treatment period).
- 6 patients dropped out of the trial at patient request.

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Baseline characteristics.

Characteristic	Esomeprazole-placebo ($N = 16$)	Placebo-esomeprazole ($N = 14$)
Median age (range) – yr	47 (19; 66)	35 (23; 59)
Female sex – no. (%)	9 (56)	6 (43)
Median body mass index (range)	22.1 (17.8; 28.4)	21.5 (17.4; 30.0)
Diagnosis		
CSA	2	1
CDA	0	3
HE	1	0
NTDT	8	5
PKD	5	3
SCD	0	2
Median markers of iron metabolism (IQR)		
Serum ferritin – µg/L	483 (302; 705)	603 (346; 807)
Serum transferrin saturation – %	59 (26; 81)	48 (31; 74)
Plasma hepcidin – µg/L	7.4 (4.2; 20.4)	11.3 (4.2; 17.7)
Median hemoglobin value (IQR) – g/dL	9.2 (7.9; 10.4)	9.7 (8.7; 10.2)
Median values of safety parameters (IQR)[a]		
Vitamin B12 – pmol/L	282 (199; 409)	275 (203; 500)
Magnesium – mmol/L	0.82 (0.81; 0.89)	0.83 (0.79; 0.88)
Median baseline LIC (IQR) – mg Fe/g dry liver weight	4.83 (3.13; 5.40)	5.44 (4.49; 8.37)

Results: safety

Event – no. (%)	Esomeprazole (*N* = 30)	Placebo (*N* = 26)
General disorder or administration-site condition		
Malaise	3 (10)	1 (4)
Fatigue	1 (3)	2 (8)
Gastro-intestinal disorder		
Nausea	1 (3)	3 (12)
Gastric pain or pyrosis	1 (3)	2 (8)
Diarrhea	6[a] (20)	2 (8)
Abdominal pain[b]	3 (10)	0 (0)
Infection or infestation		
Upper respiratory tract infection[c]	17	23
Lower respiratory tract infection[b,c]	3	4
Prosthetic valve endocarditis[b]	1 (3)	1 (4)
Sepsis eci[b]	0 (0)	1 (4)
Cholecystitis[b]	1 (3)	0 (0)
Flue (nos)	2 (7)	1 (4)
(Cardio)vascular disorder		
Vaso-occlusive crisis[b,c]	1	7
Rectus hematoma[b]	1 (3)	0 (0)
Kidney failure	0 (0)	1[a] (4)
Musculoskeletal or connective-tissue disorder		
Backpain	1[a] (3)	0 (0)

Note: Three grade 3 adverse events were reported (rapid decline in kidney function [placebo]; diarrhea in a patient diagnosed with colitis ulcerosa [esomeprazole], and severe backpain [esomeprazole]).
[a]One episode was graded grade 3 or higher.
[b]At least one serious adverse event occurred (hospitalization).
[c]Reported (number) is number of episodes.

Table 3.

- AEs occuring in >10% of patients, or graded grade 3 or higher.
- None of the patients discontinued trial participation due to AEs.
- 14 SAE occured, all hospitalization (unrelated to IMP).

Results: efficacy

	Esomeprazole mean (SD)		Placebo mean (SD)		Effect esomeprazole[a] estimate (95% confidence interval)
Primary endpoint					
Δ LIC – mg Fe/g dw	$N = 24$	−0.57 (1.20)	$N = 23$	−0.11 (0.75)	−0.55 (−1.06 to −0.05)
Secondary endpoints					
Δ Ferritin – µg/L	$N = 20$	−18 (170)	$N = 23$	18 (135)	−23 (−121 to 76)
Δ Transferrin saturation – %	$N = 22$	−1.1 (18.4)	$N = 23$	6.7 (15.9)	−7.7% (−18.8 to 3.5)

Abbreviations: Δ, delta; LIC, liver iron content; SD, standard deviation.
[a]Effect estimate of esomeprazole as calculated by linear mixed model analysis with random intercept and treatment as independent variable. Sex, iron chelator use, baseline LIC and order were included as covariates.

- In 20 of the 47 completed treatment periods (43%) pill counts and/or gastrin values indicated therapy nonadherence.
- Patients with a low hepcidin/ferritin ratio treatment with esomeprazole resulted in a significant reduction in LIC of 1.30 mg Fe/g dw (95% CI [0.54 to 2.06]; p = 0.003) larger than placebo.

Impact

- PI and co-PI presented work on several high impact meetings published in high impact hematology journal, discussed in guideline committees.
- Not mentioned in guidelines so far.
- Not easy to find due erroneous search strategy: keywords vs text words.
- Additional analyses and papers could work

Raming uitgiftes en kosten 2018-2022

	2018	2019	2020	2021	2022
V03AC01 Deferoxamine (*Desferal ®*)	136	41	89	142	254
V03AC02 Deferipron (*Ferriprox ®*)	359	378	381	418	390
V03AC03 Deferasirox (*Exjade ®*)	4.520	4.884	4.762	4.101	3.906
Totaal	**5.015**	**5.303**	**5.232**	**4.661**	**4.550**

2018	2019	2020	2021	2022
101.930	31.500	77.223	115.330	205.130
158.750	170.740	184.210	195.860	205.780
6.723.700	6.961.000	6.745.300	5.498.000	3.109.000
6.984.380	**7.163.240**	**7.006.733**	**5.809.190**	**3.519.910**

Bron: Zorginstituut Nederland / GIP
Geactualiseerd op: 24-08-2023

Lessons learned

Succesfull study; first positive RCT in CDA, HS, HE and second in PKD ever!

Recruitment was lower than expected: additional site needed to be activated

Budget Impact assessment (not discussed) small impact because the study compared placebo versus PPI and not exjade versus PPI.

Global implementation not yet, because www.pubmed.gov default search does not incorporate keywords.

Acknowledgements

Participants

Steering committee

Co-investigators

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