IJzerdeficiëntie in hartfalen
Waarom behandelen?

Dr. Niels Grote Beverborg
Cardioloog i.o.
UMCG, Groningen

Conflicts of Interest

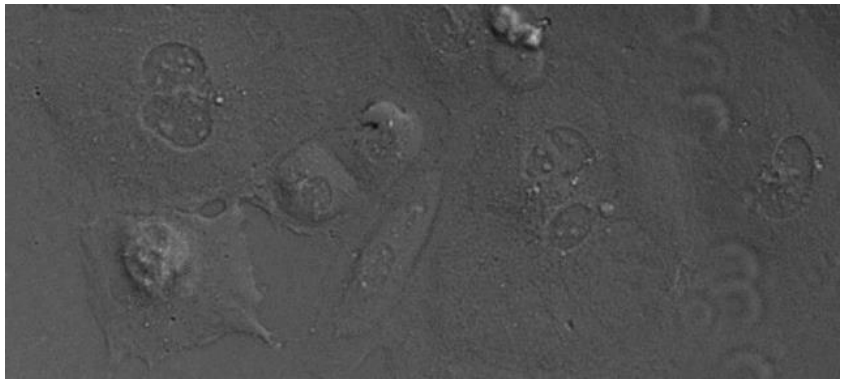
- Speaker fees from Vifor Pharma
- Research Grants from ZonMW, PLN patient foundation, AstraZeneca, Ionis Pharmaceuticals

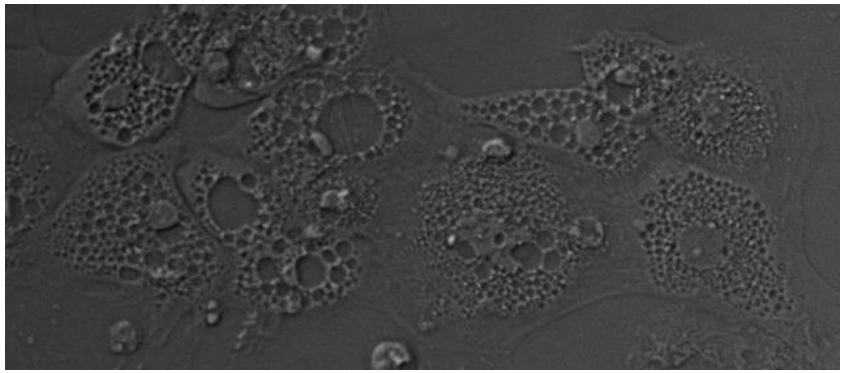
Inhoud

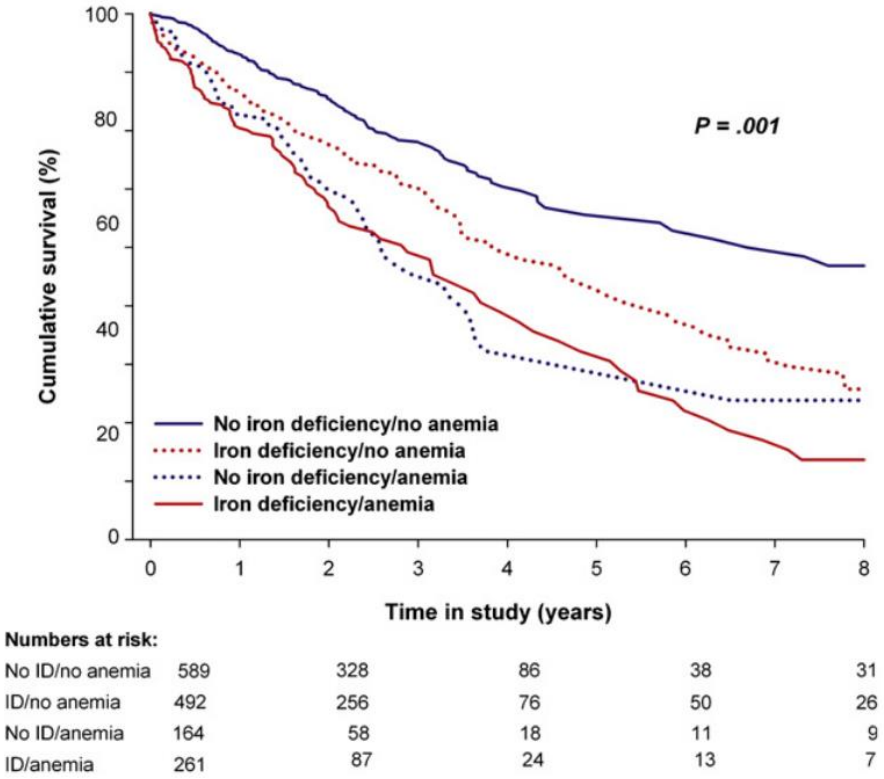
Waarom ijzerdeficiëntie behandelen?

1. Gevolgen van ijzerdeficiëntie
2. Gevolgen van behandelen
   - Orale therapie
   - Intraveneuze therapie
3. Veiligheid
4. Kosten

Gevolgen van ijzerdeficiëntie







Numbers at risk:					
No ID/no anemia	589	328	86	38	31
ID/no anemia	492	256	76	50	26
No ID/anemia	164	58	18	11	9
ID/anemia	261	87	24	13	7

Quality of life
VO_2 max
6 minute walking test
Symptoms

Orale therapie

IRONOUT-HF

Dubbelblinde, placebo-gecontroleerde studie

N=225 patiënten

LVEF<40%

IJzerdeficiënt, Hb 9 – 15 g/dL (mannen) of 9-13,5 g/dL (vrouwen)

Oraal ijzer polysaccharide 150 mg 2dd voor 16 weken

Table 3. Levels of Iron Metabolism Markers According to Treatment Group

Iron Indexes	Difference in Change From Baseline (95% CI)	*P* Value
Iron, µg/dL	11.0 (2.8 to 19.1)	.009
TIBC, µg/dL	−13.4 (−22.2 to −4.6)	.003
Tsat, %	3.3 (1.1 to 5.4)	.003
Ferritin, ng/ml	11.3 (−0.3 to 22.9)	.06
Hepcidin, ng/ml	1.5 (−0.6 to 3.7)	.17
sTfR, mg/L	−0.3 (−0.6 to −0.1)	.01

Geen verandering in:
VO_2
6MWT
NT-proBNP
Quality of life

Intraveneuze therapie

Author/year	Study name	No. patients	Blinding	ID definition	Main inclusion criteria	Study drug	Follow-up (w)	Main conclusions
Anker 2009	FAIR-HF	459	Double	ESC Guideline*	NYHA II-III LVEF<45% Hb 9.5 – 13.5g/dL	FCM	26	NYHA ↓ 6MWT ↑ EQ-5D ↑
Ponikowski 2015	CONFIRM-HF	304	Double	ESC Guideline*	NYHA II-III LVEF≤45% Hb<15g/dL	FCM	52	6MWT ↑ NYHA ↓ EQ-5D ↑
Van Veldhuisen 2017	EFFECT-HF	174	No	ESC Guideline*	NYHA II-III LVEF≤45% OMT	FCM	24	VO_2 max ↑ NYHA ↓
Ponikowski 2020	AFFIRM-AHF	1132	Double	ESC Guideline*	ADHF LVEF≤50%	FCM	52	HF-hosp ↓ CV-death ≈
Kalra 2022	IRONMAN	1137	Single	F<100 or TSAT<20%	Symptomatic HF LVEF<45%	FDM	117	HF-hops/CV-death ↓

* ESC Guideline: Ferritine < 100; Ferritine 100 – 299 + TSAT<20%
FCM: ijzer(III)carboxymaltose; FDM: ijzer(III)derisomaltose

umcg cardiology research institute

Grote Beverborg, van der Meer. FocusVasculair 2017

Intraveneuze therapie

AFFIRM-AHF

Dubbelblinde, placebogecontroleerde studie

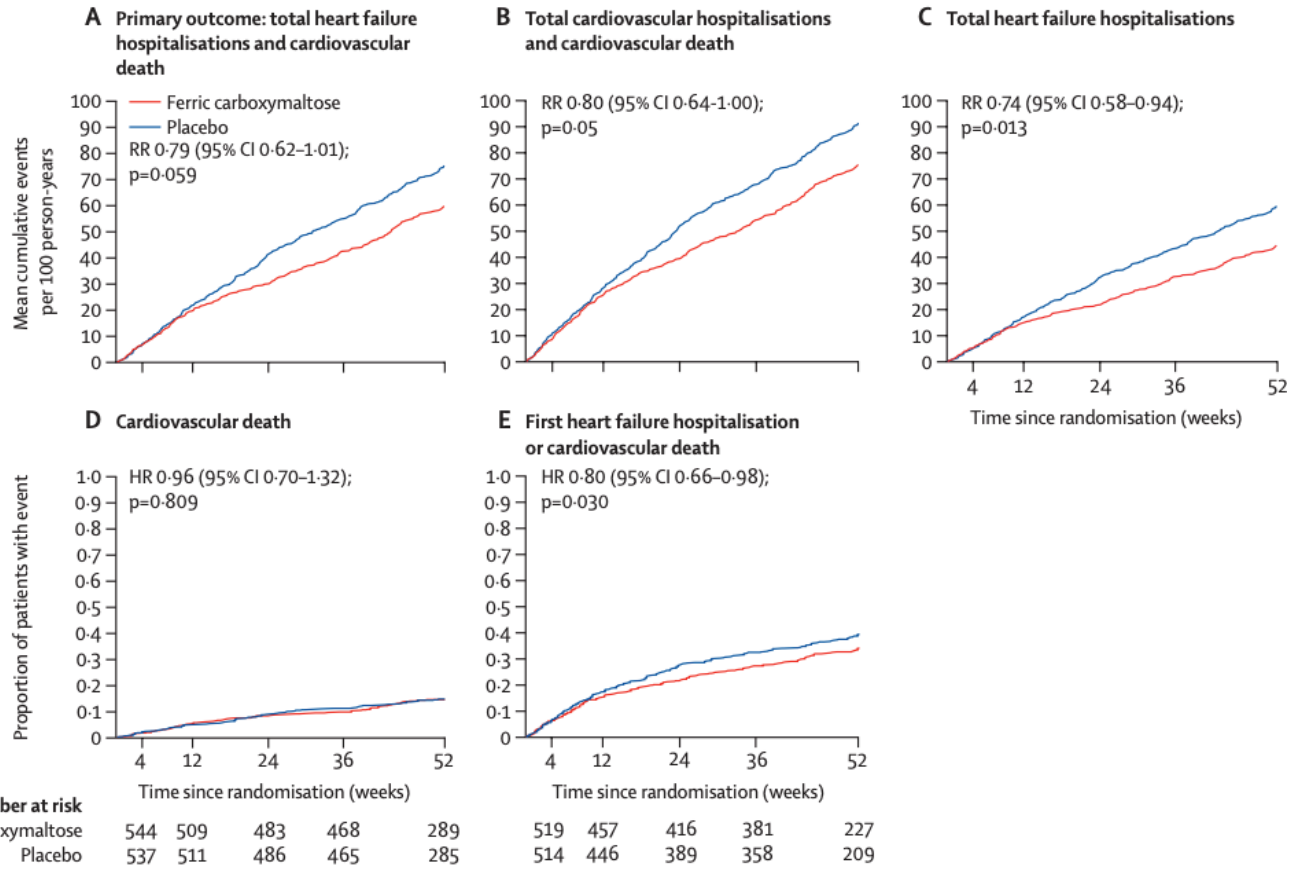
N=1132

Acuut HF, LVEF ≤50%

IJzerdeficiëntie: F<100 of F 100-300 + T<20

1:1 FCM (iv) versus placebo voor 24 weken

Eindpunt: HF-hospitalisaties + CV overlijden



umcg cardiology research institute

Ponikowski et al. Lancet 2020

Intraveneuze therapie

AFFIRM-AHF

Dubbelblinde, placebogecontroleerde studie

N=1132

Acuut HF, LVEF ≤50%

IJzerdeficiëntie: F<100 of F 100-300 + T<20

1:1 FCM (iv) versus placebo voor 24 weken

Eindpunt: HF-hospitalisaties + CV overlijden

	Ferric carboxymaltose (n=558)		Placebo (n=550)		Hazard ratio (95% CI)	p value
	Number of events (%)	Rate per 100 patient-years	Number of events (%)	Rate per 100 patient-years		
Modified intention-to-treat analysis						
First heart failure hospitalisation or cardiovascular death	181 (32%)	37·40	209 (38%)	47·10	0·80 (0·66–0·98)	0·030
Cardiovascular death	77 (14%)	15·90	78 (14%)	16·10	0·96 (0·70–1·32)	0·81
COVID-19 sensitivity analysis*						
First heart failure hospitalisation or cardiovascular death	175 (31%)	44·59	205 (37%)	52·20	0·79 (0·65–0·97)	0·023
Cardiovascular death	73 (13%)	16·13	76 (14%)	16·78	0·94 (0·68–1·29)	0·69

*Patients were censored in each country on the date when the first patient with COVID-19 was reported in the respective country.

Table 3: **Time to first event outcomes**

umcg cardiology research institute

Ponikowski et al. Lancet 2020

Intraveneuze therapie

IRONMAN

Open-labelstudie met geblindeerde uitkomstmaten

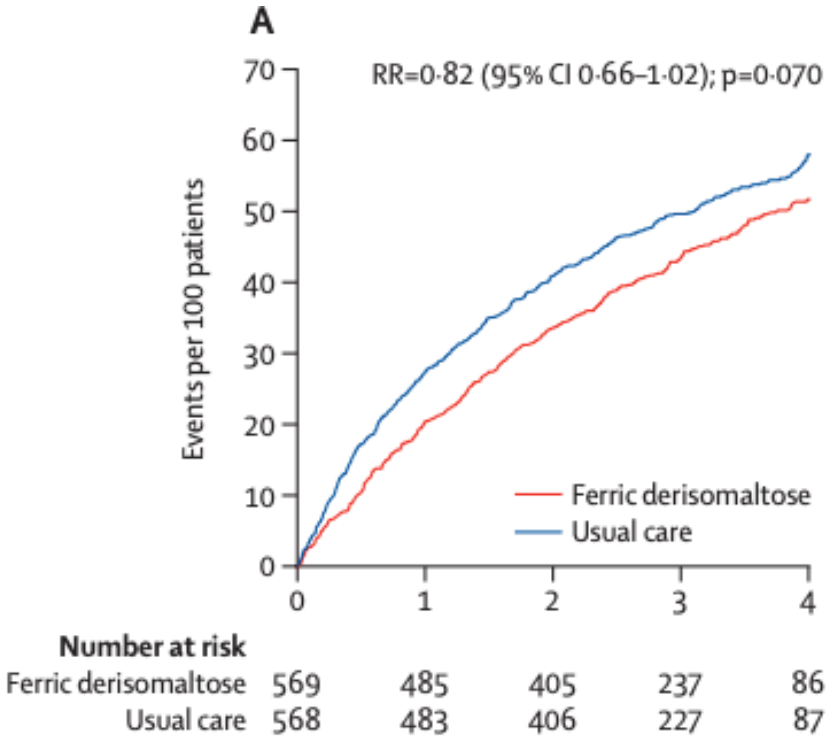
N=1137

HFrEF, LVEF <45%

IJzerdeficiëntie: T<20% of F<100

1:1 FDM (iv) versus standaardzorg

Eindpunt: HF-hospitalisatie + CV overlijden



Kalra et al. Lancet 2022

Intraveneuze therapie

IRONMAN

Open-labelstudie met geblindeerde uitkomstmaten

N=1137

HFrEF, LVEF <45%

IJzerdeficiëntie: T<20% of F<100

1:1 FDM (iv) versus standaardzorg

Eindpunt: HF-hospitalisatie + CV overlijden

	Ferric derisomaltose group (n=527)	Usual care group (n=536)	Estimated treatment effect (95% CI)	p value
Primary endpoint				
Cardiovascular death and hospital admission for heart failure, number of events (rate per 100 patient-years)	210 (22·3)	280 (29·3)	0·76 (0·58–1·00)*	0·047
Secondary endpoints				
Hospital admissions for heart failure, number of events (rate per 100 patient-years)	163 (17·3)	218 (22·8)	0·76 (0·56–1·03)*	0·077
Cardiovascular hospital admission, n (%)	177 (34%)	205 (38%)	0·86 (0·70–1·05)†	0·14
Cardiovascular death or hospital admission for heart failure, n (%)	127 (24%)	160 (30%)	0·80 (0·63–1·01)†	0·055
Cardiovascular death, n (%)	67 (13%)	86 (16%)	0·79 (0·57–1·09)†	0·15
Cardiovascular death or hospital admission for stroke, myocardial infarction, or heart failure, n (%)	137 (26%)	175 (33%)	0·78 (0·62–0·98)†	0·030
All-cause mortality, n (%)	103 (20%)	115 (21%)	0·91 (0·70–1·19)†	0·48
All-cause hospital admission, n (%)	260 (49%)	288 (54%)	89 (0·75–1·05)†	0·18
All-cause mortality or all-cause unplanned hospital admission, n (%)	271 (51%)	303 (57%)	0·89 (0·75 to 1·04)†	0·15

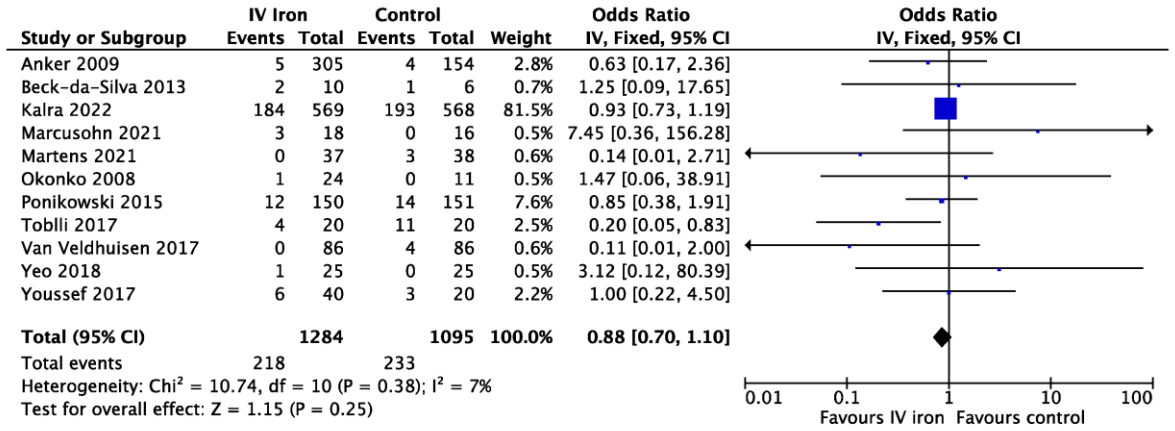
All comparisons are of the ferric derisomaltose group with the usual care group. *Rate ratio (estimated using the method of Lin and colleagues[12]). †Hazard ratio (estimated from Cox proportional hazards models).

Table 4: **Primary and secondary endpoints in the COVID-19 analysis, censoring follow-up on Sept 30, 2020**

umcg cardiology research institute

Kalra et al. Lancet 2022

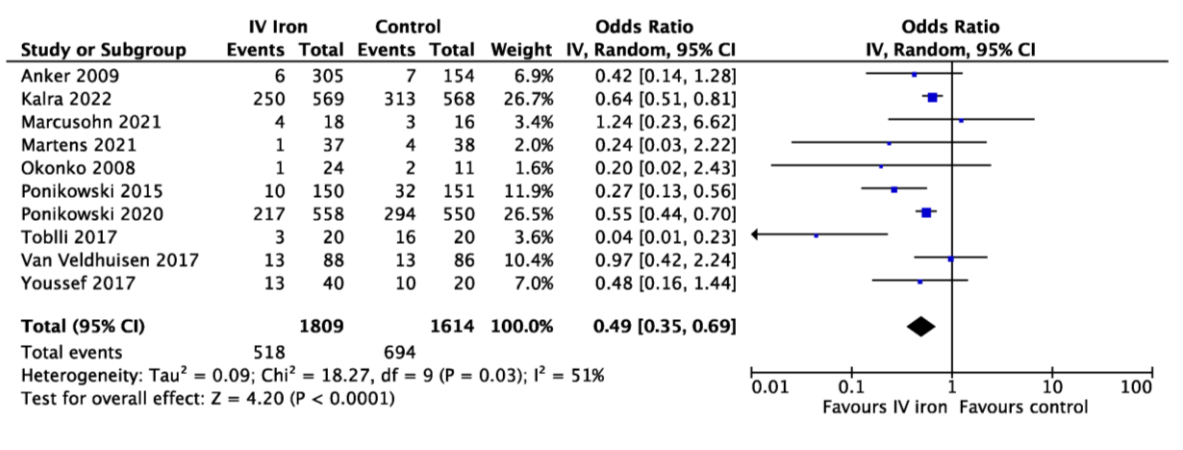
Intraveneuze therapie



Study or Subgroup	IV Iron Events	IV Iron Total	Control Events	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Anker 2009	5	305	4	154	2.8%	0.63 [0.17, 2.36]
Beck-da-Silva 2013	2	10	1	6	0.7%	1.25 [0.09, 17.65]
Kalra 2022	184	569	193	568	81.5%	0.93 [0.73, 1.19]
Marcusohn 2021	3	18	0	16	0.5%	7.45 [0.36, 156.28]
Martens 2021	0	37	3	38	0.6%	0.14 [0.01, 2.71]
Okonko 2008	1	24	0	11	0.5%	1.47 [0.06, 38.91]
Ponikowski 2015	12	150	14	151	7.6%	0.85 [0.38, 1.91]
Toblli 2017	4	20	11	20	2.5%	0.20 [0.05, 0.83]
Van Veldhuisen 2017	0	86	4	86	0.6%	0.11 [0.01, 2.00]
Yeo 2018	1	25	0	25	0.5%	3.12 [0.12, 80.39]
Youssef 2017	6	40	3	20	2.2%	1.00 [0.22, 4.50]
Total (95% CI)		**1284**		**1095**	**100.0%**	**0.88 [0.70, 1.10]**
Total events	218		233			

Heterogeneity: $Chi^2 = 10.74$, df = 10 (P = 0.38); $I^2 = 7\%$
Test for overall effect: Z = 1.15 (P = 0.25)

All-cause mortality



Study or Subgroup	IV Iron Events	IV Iron Total	Control Events	Control Total	Weight	Odds Ratio IV, Random, 95% CI
Anker 2009	6	305	7	154	6.9%	0.42 [0.14, 1.28]
Kalra 2022	250	569	313	568	26.7%	0.64 [0.51, 0.81]
Marcusohn 2021	4	18	3	16	3.4%	1.24 [0.23, 6.62]
Martens 2021	1	37	4	38	2.0%	0.24 [0.03, 2.22]
Okonko 2008	1	24	2	11	1.6%	0.20 [0.02, 2.43]
Ponikowski 2015	10	150	32	151	11.9%	0.27 [0.13, 0.56]
Ponikowski 2020	217	558	294	550	26.5%	0.55 [0.44, 0.70]
Toblli 2017	3	20	16	20	3.6%	0.04 [0.01, 0.23]
Van Veldhuisen 2017	13	88	13	86	10.4%	0.97 [0.42, 2.24]
Youssef 2017	13	40	10	20	7.0%	0.48 [0.16, 1.44]
Total (95% CI)		**1809**		**1614**	**100.0%**	**0.49 [0.35, 0.69]**
Total events	518		694			

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 18.27$, df = 9 (P = 0.03); $I^2 = 51\%$
Test for overall effect: Z = 4.20 (P < 0.0001)

HF hospitalizations

Veiligheid

AFFIRM-AHF

12 Summary overview of adverse event reporting

Adverse event reporting	FCM (n=559)		Placebo (n=551)	
	n (%)	events n	n (%)	events n
Reported adverse events	357 (63.9)	1246	360 (65.3)	1314
Reported serious adverse events	250 (44.7)	547	282 (51.2)	632
Adverse events leading to withdrawal of study treatment	61 (10.9)	71	79 (14.3)	88
Adverse event leading to study discontinuation	98 (17.5)	117	96 (17.4)	123
Adverse event leading to hospitalization	226 (40.4)	483	257 (46.6)	561
Adverse events of interest by MedDRA System Organ Class				
Cardiac Disorders	224 (40.1)	391	244 (44.3)	453
Infections and Infestations	102 (18.2)	143	121 (22.0)	165
Gastrointestinal	64 (11.4)	99	59 (10.7)	94
Diarrhoea	17 (3.0)	19	14 (2.5)	16
Constipation	10 (1.8)	10	10 (1.8)	12
Metabolism and nutrition disorder	45 (8.1)	74	85 (10.5)	102
Hypophosphataemia	1 (0.2)	1	1 (0.2)	1
Muskuloskeletal and connective tissue disorders	24 (4.3)	29	28 (5.1)	33
Bone pain	0 (0)	0	1 (0.2)	1
Skin and subcutaneous tissue disorders	13 (2.3)	14	12 (2.2)	14
Pruritus	3 (0.5)	3	3 (0.5)	3
Rash	2 (0.4)	2	2 (0.4)	2
Urticaria	1 (0.2)	1	1 (0.2)	1
Neoplasms bening, malignant, and unspecified	9 (1.6)	13	7 (1.3)	9
Immune system disroders	3 (0.5)	3	1 (0.2)	1
Drug hypersensitivity	2 (0.4)	2	0 (0)	0
Hypersensitivity	0	0	1 (0.2)	1

Table legend: Data are for the Safety population data set. Data are number of patients with at least one event (%) and total number of events reported. MedDRA denotes Medical Dictionary for Regulatory Activities

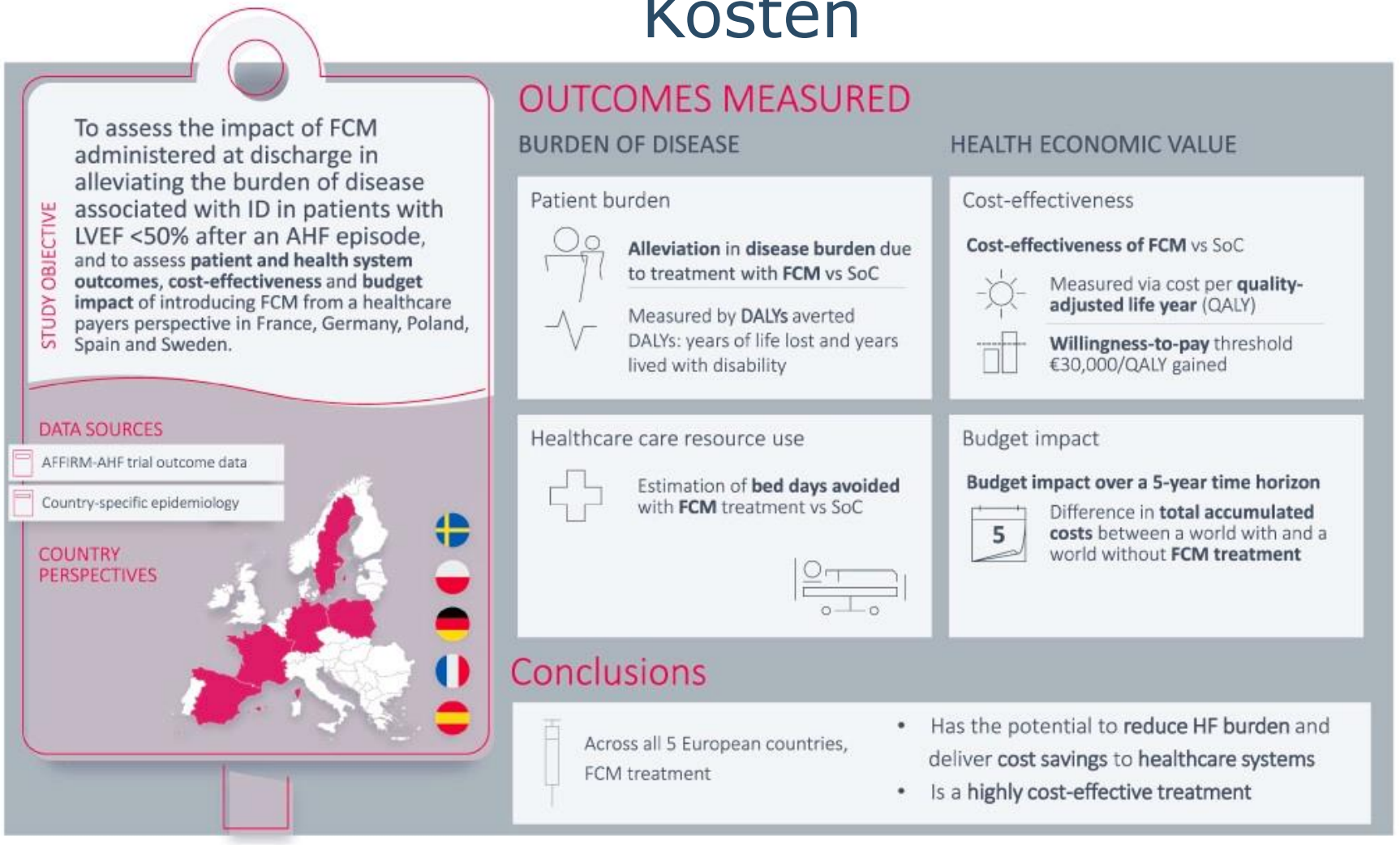
IRONMAN

	Ferric derisomaltose group (n=559)	Usual care group (n=568)	Difference (95% CI)	p value
Serious adverse events by system organ class, n (%)				
All	410 (73%)	435 (77%)	−3·24 (−8·30 to 1·82)	0·21
Cardiac	200 (36%)	243 (43%)	−7·00 (−12·69 to −1·32)	0·016
Infections and infestations	142 (25%)	162 (29%)	−3·12 (−8·30 to 2·06)	0·24
Surgical and medical	80 (14%)	74 (13%)	1·28 (−2·73 to 5·29)	0·53
Gastrointestinal	56 (10%)	64 (11%)	−1·25 (−4·85 to 2·35)	0·50
Injury, poisoning, and procedural	59 (11%)	63 (11%)	−0·54 (−4·16 to 3·09)	0·77
Respiratory, thoracic, and mediastinal	48 (9%)	67 (12%)	−3·21 (−6·74 to 0·32)	0·074
Renal and urinary	55 (10%)	64 (11%)	−1·43 (−5·01 to 2·16)	0·43
General and administration site	57 (10%)	52 (9%)	1·04 (−2·41 to 4·49)	0·55
Nervous system	54 (10%)	45 (8%)	1·74 (−1·57 to 5·04)	0·30
Metabolism and nutrition	31 (6%)	49 (9%)	−3·08 (−6·07 to −0·09)	0·043
Vascular disorders	34 (6%)	42 (7%)	−1·31 (−4·24 to 1·61)	0·38
Neoplasms benign, malignant, and unspecified	22 (4%)	21 (4%)	0·24 (−2·00 to 2·48)	0·83
Musculoskeletal and connective tissue	19 (3%)	25 (4%)	−1·00 (−3·26 to 1·26)	0·38
Prespecified safety endpoints				
Deaths due to infection, n (%)	34 (6%)	28 (5%)	1·22 (0·74 to 2·02)*	0·43
Hospitalisations due to infection, n (rate per 100 patient-years)	175 (11·7)	213 (14·2)	0·82 (0·62 to 1·08)†	0·16

Values are numbers of patients with at least one event in each category. *Hazard ratio (estimated using a Cox proportional hazards model). †Rate ratio (estimated using a negative binomial regression model).

Table 3: **Serious adverse events by Medical Dictionary for Regulatory Activities system organ class and prespecified safety endpoints**

Kosten


STUDY OBJECTIVE
To assess the impact of FCM administered at discharge in alleviating the burden of disease associated with ID in patients with LVEF <50% after an AHF episode, and to assess **patient and health system outcomes, cost-effectiveness** and **budget impact** of introducing FCM from a healthcare payers perspective in France, Germany, Poland, Spain and Sweden.
DATA SOURCES
AFFIRM-AHF trial outcome data
Country-specific epidemiology
COUNTRY PERSPECTIVES
OUTCOMES MEASURED
BURDEN OF DISEASE
HEALTH ECONOMIC VALUE
Patient burden
Alleviation in **disease burden** due to treatment with **FCM** vs SoC
Measured by **DALYs** averted
DALYs: years of life lost and years lived with disability
Cost-effectiveness
Cost-effectiveness of FCM vs SoC
Measured via cost per **quality-adjusted life year** (QALY)
Willingness-to-pay threshold €30,000/QALY gained
Healthcare care resource use
Estimation of **bed days avoided** with **FCM** treatment vs SoC
Budget impact
Budget impact over a 5-year time horizon
5
Difference in **total accumulated costs** between a world with and a world without **FCM treatment**
Conclusions
Across all 5 European countries, FCM treatment
• Has the potential to **reduce HF burden** and deliver **cost savings** to **healthcare systems**
• Is a **highly cost-effective treatment**

Toekomstige trials

FAIR-HF2

FCM in HFrEF, N=1200

Eindpunt: CV overlijden, HF heropnames

HEART-FID

FCM in HFrEF, N=3014

Eindpunt: overlijden, HF opnames, 6MWT

FAIR-HFpEF

FCM in HFpEF, N=200

Eindpunt: 6MWT

Conclusie

Waarom ijzerdeficiëntie behandelen?

1. Gevolgen deficiëntie → verminderde QoL, inspanning en prognose
2. Gevolgen behandelen
   - Orale therapie → minimaal effect op biomarkers
   - IV-therapie → positief effect op QoL, inspanning en HF opnames in HFrEF
3. Veiligheid → behandeling wordt goed verdragen
4. Kosten → kosteneffectieve behandeling