REFEEDING SYNDROM HOS KRITISK SYGE – NY VIDEN FRA ET RANDOMISERET FORSØG

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CONFLICTS OF INTEREST

Grants: ESPEN, Copenhagen University Hospital, Fresenius Kabi, MedGraphics, COSMED

Lectures: Fresenius Kabi, Baxter, Nutricia

Bonds: None

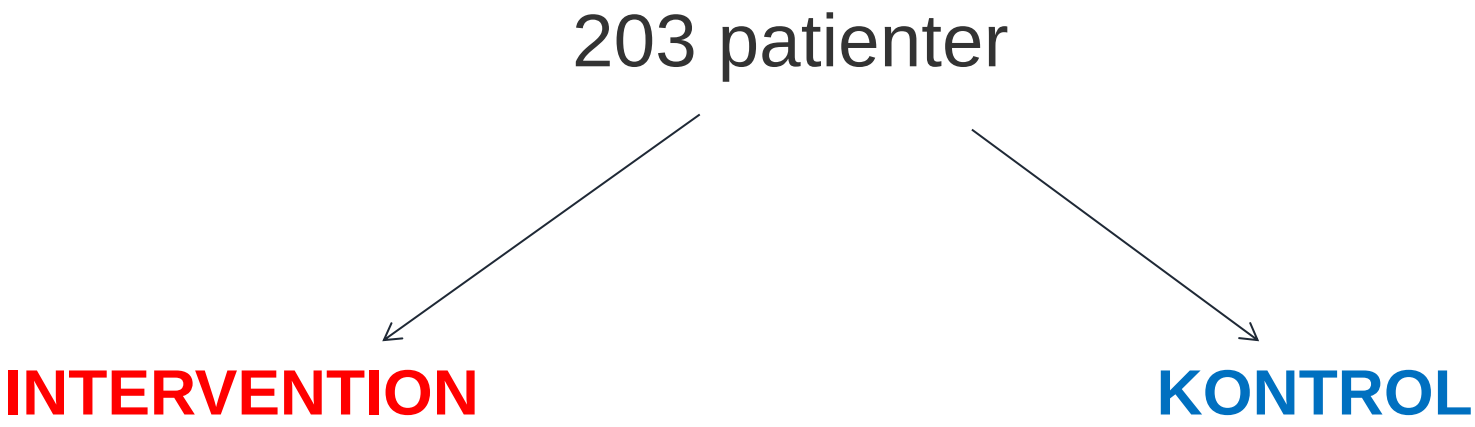
Intensiv Terapiklinik 4131, Rigshospitalet

- Multidisciplinær intensivafdeling
- 25 respiratorpladser
- Årligt 1200+ indlagte patienter
- Gennemsnitlig ICU mortalitet 13% (Range 3 - 53 %)

- Patientkategorier: Sepsis/SIRS, ambustio multiplex, lever tx, necrotiserende fascitiis, traumer, abdominalkirurgi og meget andet…..

EAT-ICU TRIAL

Tidlig målrettet ernæring til intensivpatienter

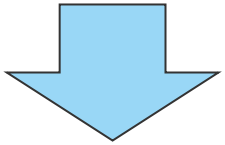


Def. Refeeding Syndrom:

Potentiel fatal tilstand med akut udvikling af elektrolytmangel, væskeretention og forskydning af glukose-homeostasen (Crook et al. 2001).

The Fasting-state:

1. Depletering af hepatisk glykogendepot
2. Metabolisering af adipøst- og muskelvæv
3. Nedsat insulin sekretion



Intracellulært tab af elektrolytter

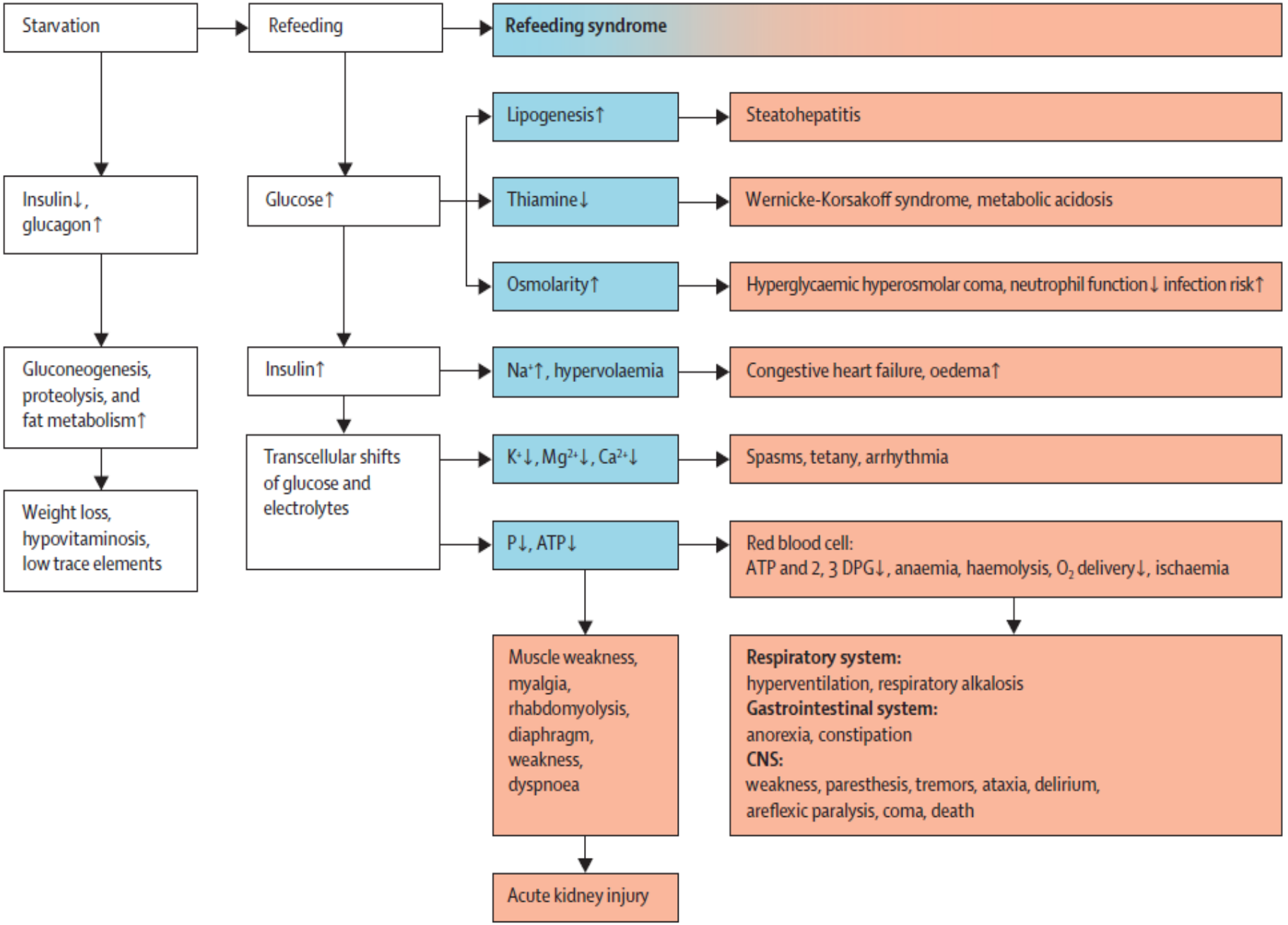
Afsløres ikke nødvendigvis i blodprøve

Initiel derrangering

- HYPOFOSFATÆMI
- Elektrolytforstyrrelser
- Væskeretention
- Hyperglykæmi
- Vitaminmangel (thiamin)

Kliniske implikationer

- ✓Resp. Insuff., udtrætning af diafragma muskulatur
- ✓Spasmer, kramper, arytmier
- ✓Hjertesvigt
- ✓Delir
- ✓Infektiøse komplikationer
- ✓Wernicke’s encephalopati
- ✓Død


Starvation
Refeeding
Refeeding syndrome
Insulin↓, glucagon↑
Glucose↑
Lipogenesis↑
Steatohepatitis
Thiamine↓
Wernicke-Korsakoff syndrome, metabolic acidosis
Osmolarity↑
Hyperglycaemic hyperosmolar coma, neutrophil function↓ infection risk↑
Gluconeogenesis, proteolysis, and fat metabolism↑
Insulin↑
Na+↑, hypervolaemia
Congestive heart failure, oedema↑
Transcellular shifts of glucose and electrolytes
K+↓, Mg2+↓, Ca2+↓
Spasms, tetany, arrhythmia
P↓, ATP↓
Red blood cell:
ATP and 2, 3 DPG↓, anaemia, haemolysis, O2 delivery↓, ischaemia
Weight loss, hypovitaminosis, low trace elements
Muscle weakness, myalgia, rhabdomyolysis, diaphragm, weakness, dyspnoea
Respiratory system:
hyperventilation, respiratory alkalosis
Gastrointestinal system:
anorexia, constipation
CNS:
weakness, paresthesis, tremors, ataxia, delirium, areflexic paralysis, coma, death
Acute kidney injury

INCIDENS?

Ref.	Population	n	Def.	Incidens, %
Daily et al.	Traume	12	<0,80 mmol/l	75
Zazzo et al.	Kirurgisk ITA	208	<0,80 mmol/l	28,8
Berger et al.	Ambustio	16	<0,80 mmol/l	100
Barak et al.	Sepsis	99	<0,80 mmol/l	80
Bech et al.	ITA	290	<0,60 mmol/l	24
Suzuki et al.	ITA	2730	<0,60 mmol/l	20

REGION

Hvem skal vi lede efter?

Risikofaktorer:

- ✓ Underernæring
- ✓ D-vitaminmangel
- ✓ Opkast/diarre
- ✓ Dialysebehandling/diuretika
- ✓ Renale tubulære defekter
- ✓ Metabolisk acidose
- ✓ Steroidbehandling
- ✓ Respiratorisk alkalose
- ✓ Glukose-/insulinbehandling
- ✓ Katekolaminbehandling

61-årig kvinde, 35 kg, BMI 14
Osteoradionekrose bilat. i underkæbe
K, Na, Mg, F normale
REE målt med IC: 712 kcal/døgn

MONITORERING af p-fosfat på intensiv?

- ✓Dagligt – 46 %
- ✓1-3 x ugt. – 42 %
- ✓Klinisk indikation – 12 %

Geerse DA et al., Neth J med, 2012

BEHANDLING af hypofosfatæmi på intensiv?

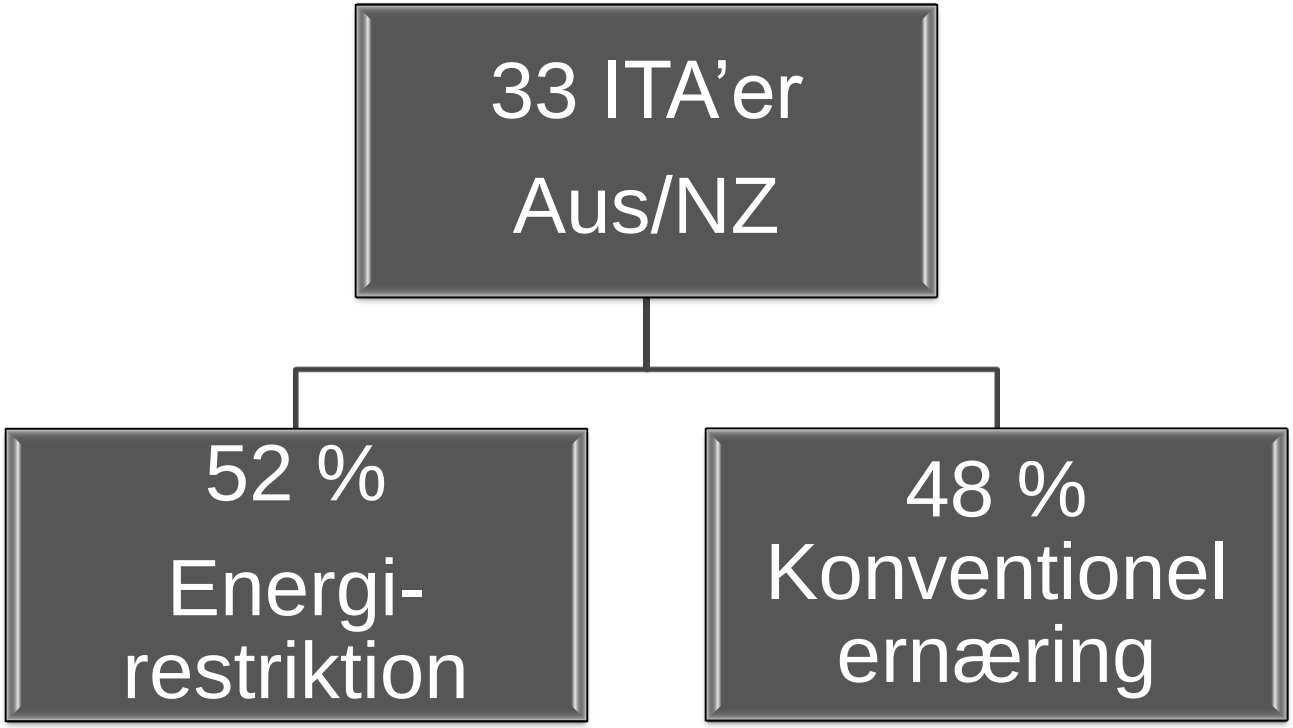
Ingen randomiserede, kontrollerede interventionsstudier!

Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial

*Gordon S Doig, Fiona Simpson, Philippa T Heighes, Rinaldo Bellomo, Douglas Chesher, Ian D Caterson, Michael C Reade, Peter W J Harrigan, for the Refeeding Syndrome Trial Investigators Group**

REGION

Baggrund - survey



Simpson F. et al, Am J Resp Crit Care Med, 2009.

Formål

- Adressere tvivlen hos klinikeren vedr. ernæringsterapi ved RS
- Teste effekten af energirestriktion på relevante kliniske effektmål sammenlignet med standard care

Design

- Multicenterforsøg på 13 ITA'er (11 Aus / 2 NZ)
- Enkelt-blindet RCT med randomisering 1:1
- Stratificeret efter:
  - Fosfat: > 0,32 mmol/l vs. ≤ 0,32 mmol/l
  - BMI: > 18 vs. ≤ 18
- Computer randomisering med variabel blokstørrelse og skjult allokering, power beregning og ITT-analyse

Inklusion

- Voksne patienter

- S-fosfat < 0,65 mmol/l i løbet af 72 efter start af ernæring

OG

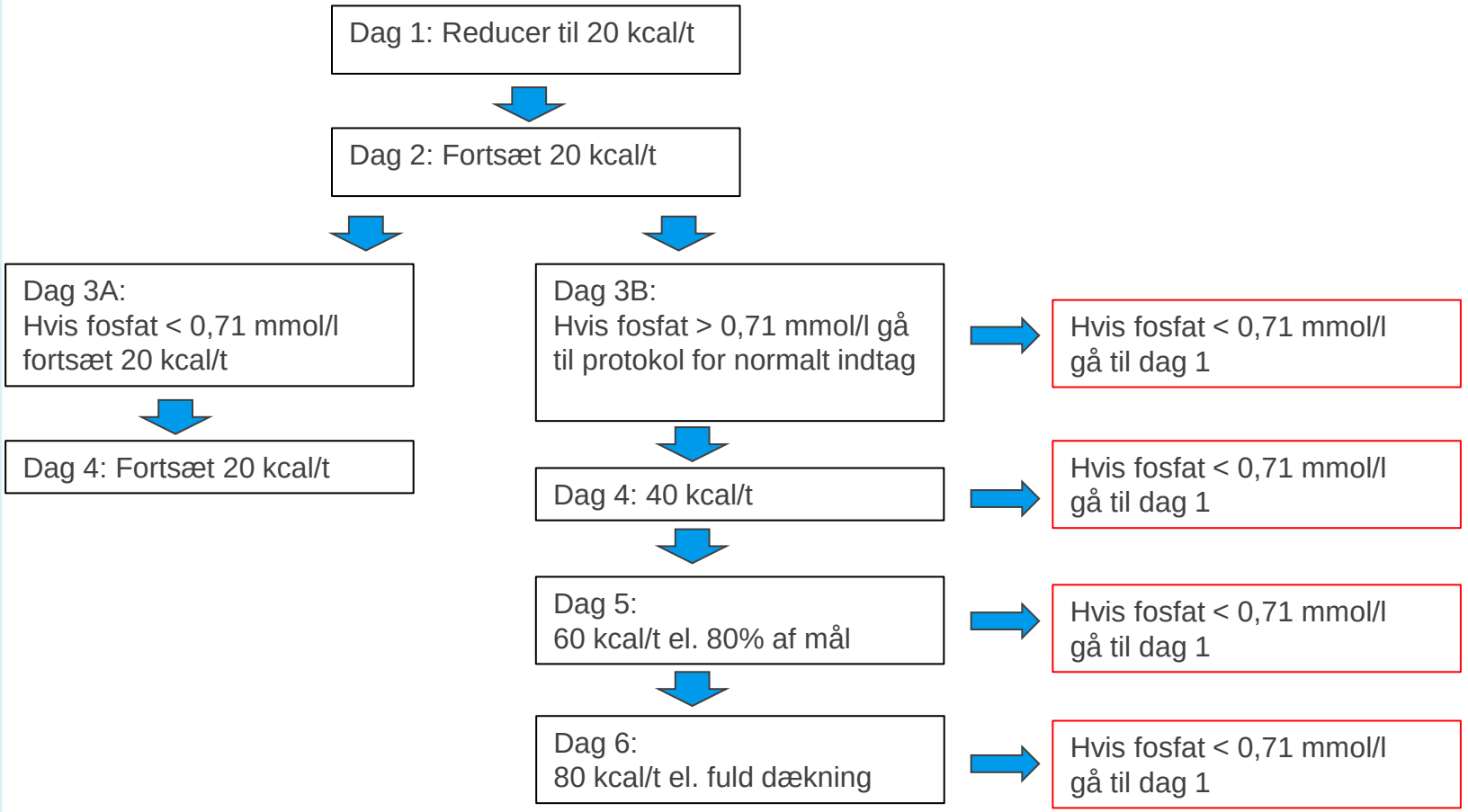
- Fald i s-fosfat > 0,16 mmol/l fra tidligere målt værdi

Eksklusion

- Pågående dialyse
- Nylig parathyroidektomi
- I behandling for hyperfosfatæmi

Rigshospitalet

Intervention - kalorierestriktion



Kontrolgruppe

Standard of care

Substitutionsprotokol

Appendix S3: Phosphate Replacement Protocol: Phosphate dosing table.

	Patient weight			
Serum Phosphate	40 - 60kg	61 - 80kg	81 - 120kg	> 120kg
0·71 to 0·55 mmol/L	10 mmol Phosphate IV over 6 hours*	15 mmol Phosphate IV over 6 hours*	20 mmol Phosphate IV over 6 hours*	25 mmol Phosphate IV over 6 hours*
0·54 to 0·32 mmol/L	20 mmol Phosphate IV over 6 hours*	30 mmol Phosphate IV over 6 hours*	40 mmol Phosphate IV over 6 hours*	50 mmol Phosphate IV over 6 hours*
below 0·32 mmol/L	30 mmol Phosphate IV over 6 hours*	40 mmol Phosphate IV over 6 hours*	50 mmol Phosphate IV over 6 hours*	60 mmol Phosphate IV over 6 hours*

Primært endpoint

Antal dage i live efter udskrivelse fra ITA ved 60 dages follow-up

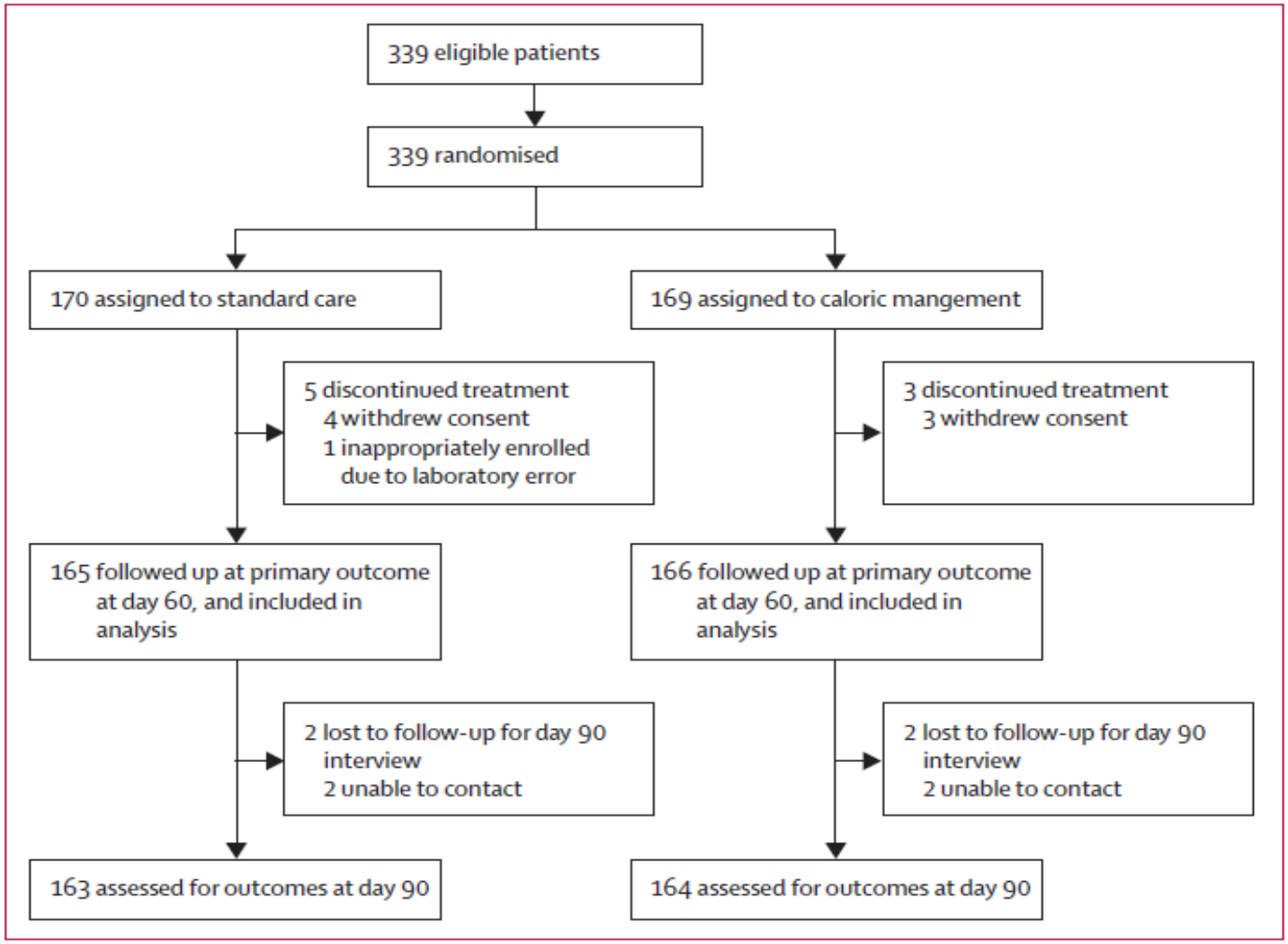
Udgjort af:

- ICU LOS
- Overall survival time
- Mortalitet ved 60 dages follow-up

Sekundære endpoints

- ✓Infektiøse komplikationer
- ✓Behov for antibiotisk behandling
- ✓Insulinbehov
- ✓BS
- ✓Daglig dosis fosfat subst.
- ✓Laveste daglig fosfat og kalium
- ✓Antal dages organdysfunktion
- ✓Øvrige concomitante ITA-behandlinger

Consort


339 eligible patients
339 randomised
170 assigned to standard care
169 assigned to caloric mangement
5 discontinued treatment
4 withdrew consent
1 inappropriately enrolled due to laboratory error
3 discontinued treatment
3 withdrew consent
165 followed up at primary outcome at day 60, and included in analysis
166 followed up at primary outcome at day 60, and included in analysis
2 lost to follow-up for day 90 interview
2 unable to contact
2 lost to follow-up for day 90 interview
2 unable to contact
163 assessed for outcomes at day 90
164 assessed for outcomes at day 90

Patientkarakteristika

	Standard care (n=165 patients)	Caloric management (n=166 patients)
Age (years)	61 (16)	59 (16)
Sex		
Female	61 (37%)	73 (44%)
Male	104 (63%)	93 (56%)
APACHE II score[22]	18 (6)	18 (6)
Mechanically ventilated	150 (91%)	152 (92%)
BMI (kg/m²)		
Mean	28 (6·7)	28 (7·3)
<18 kg/m²	5 (3%)	6 (4%)
SGA		
Muscle wasting	1·3 (0·7)	1·4 (0·8)
Fat loss	1·4 (0·7)	1·5 (0·8)
Risk factors for refeeding-related hypophosphataemia		
Calories per h (EN, PN, and glucose) at time of enrolment (kcal/h)	69 (20)	68 (19)
Total caloric intake (EN, PN, and glucose) 24 h before enrolment (kcal)	1188 (533)	1180 (526)
Days since feeding started in ICU	1·4 (0·7)	1·3 (0·7)
Days in ICU before enrolment	2·4 (1·2)	2·3 (1·2)
Days in hospital before enrolment	4·0 (4·3)	4·0 (4·8)
Serum phosphate at study entry (mmol/L)	0·5 (0·1)	0·5 (0·1)
Serum potassium at study entry (mmol/L)	3·9 (0·5)	3·9 (0·5)
Lowest blood glucose in previous 24 h (mmol/L)	7·4 (1·7)	6·9 (1·5)
Highest blood glucose in previous 24 h (mmol/L)	10·7 (32·8)	10·6 (32·7)
Lowest serum albumin in previous 24 h (g/L)	25·4 (65·8)	25·0 (65·7)
Maximum insulin infusion rate (units per h)	5·6 (4·3)*	5·0 (3·8)†
Semipermanent (surgically placed) feeding tube	11 (7%)	19 (12%)
History of high alcohol intake‡	22 (13%)	18 (11%)
Distal loop diuretic (administered in previous 24 h)	57 (35%)	41 (25%)
Long term or high dose corticosteroids	8 (5%)	9 (5%)
Respiratory alkalosis§	35 (21%)	33 (20%)
Creatinine (µmol/L)	84 (47)	84 (43)

Resultater - Primært endpoint

39·9 (95% CI 36·4–43·7) for standard care

compared with

44·8 days (40·9–49·1) ved energirestriktion

Mean difference of 4·9 days (–2·3 to 13·6, **p=0·19**)

Også ved adjustet analyse!

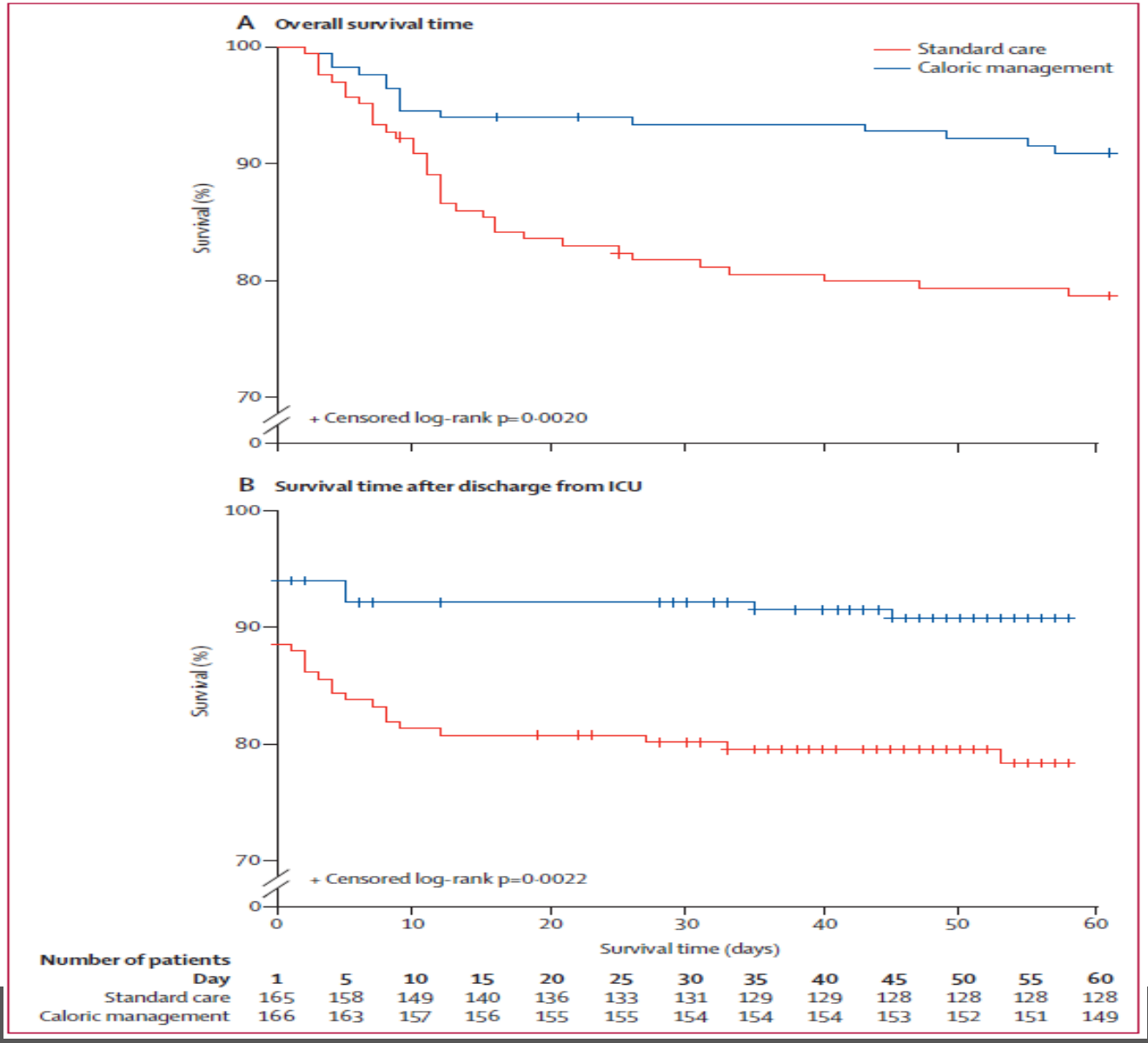
Resultater – fortsat

	Standard care (n=165 patients)	Caloric management (n=166 patients)	Risk difference (95% CI)	p value
Vital status (% alive)				
ICU discharge status	150/165 (91%)	157/166 (95%)	3·7% (−5·3 to 12·7)	0·20
Hospital discharge status	135/165 (82%)	151/166 (91%)	9·2% (0·7 to 17·7)	0·017
Day 60 status	128/163 (79%)*	149/164 (91%)*	12·3% (3·9 to 20·7)	0·002
Day 90 status	128/163 (79%)*	143/164 (87%)*	8·7% (0·04 to 17·0)	0·041
Length of stay (days)				
ICU	10·0 (9·2 to 10·9)	11·4 (10·5 to 12·4)	1·4 (−0·42 to 3·5)	0·14
Hospital	21·7 (20·0 to 23·5)	27·9 (25·7 to 30·3)	6·2 (2·0 to 11·2)	0·003
Quality of life and physical function scores† (n responses available for analysis)				
RAND-36 general health	53·4 (22·6; n=124/128)	46·0 (26·0 n=136/143)	−7·5 (−13·4 to −1·5)	0·014
ECOG performance status	1·3 (1·0; n=125/128)	1·5 (1·1; n=135/143)	0·18 (−0·06 to 0·43)	0·18
RAND-36 physical function	47·3 (35·0; n=123/128)	40·9 (33·4; n=135/143)	−6·4 (−14·8 to 2·0)	0·13

Data are n/N (%), mean (95% CI), and mean (SD), unless otherwise stated. ICU=intensive care unit. RAND=the RAND Corporation.[13] ECOG=Eastern Collaborative Oncology Group. *Four patients could not be contacted after hospital discharge (two in the standard care and two in the caloric management group). †Reported by survivors at day 90 interview.

Table 2: **Vital status, length of stay, and quality of life interviews**

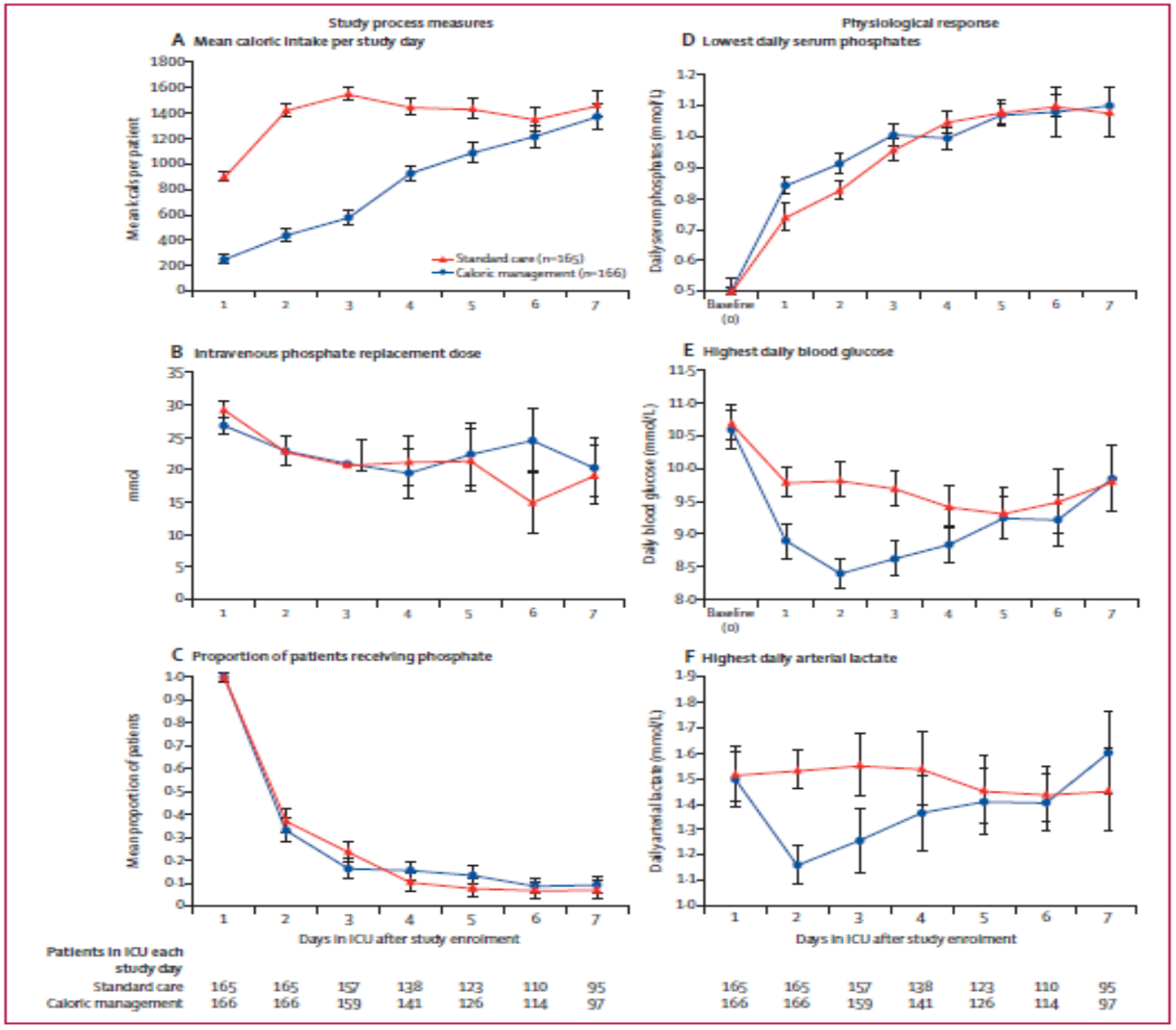
Resultater – fortsat



Number of patients

Day	1	5	10	15	20	25	30	35	40	45	50	55	60
Standard care	165	158	149	140	136	133	131	129	129	128	128	128	128
Caloric management	166	163	157	156	155	155	154	154	154	153	152	151	149

Resultater


Study process measures
A Mean caloric intake per study day
Mean cals per patient
Standard care (n=165)
Caloric management (n=166)
B Intravenous phosphate replacement dose
mmol
C Proportion of patients receiving phosphate
Mean proportion of patients
Days in ICU after study enrolment
Physiological response
D Lowest daily serum phosphates
Daily serum phosphates (mmol/L)
Baseline (0)
E Highest daily blood glucose
Daily blood glucose (mmol/L)
F Highest daily arterial lactate
Daily arterial lactate (mmol/L)
Days in ICU after study enrolment
Patients in ICU each study day
Standard care 165 165 157 138 123 110 95
Caloric management 166 166 159 141 126 114 97
165 165 157 138 123 110 95
166 166 159 141 126 114 97

Resultater – fortsat

	Standard care (165 patients)	Caloric management (166 patients)	Risk difference (95% CI)	p value
Catheter*	4 (2%)	4 (2%)	0·0% (−10·7 to 10·7)	1·00
Catheter tip*	4 (2%)	4 (2%)	0·0% (−10·7 to 10·7)	1·00
Surgical wound	4 (2%)	1 (0·6%)	−1·8% (−12·5 to 8·9)	0·21
Bloodstream	8 (5%)	2 (1%)	−3·6% (−7·1 to 0·0)	0·06
Abdominal	1 (0·6%)	0	−0·61% (−1·8 to 0·6)	0·50
Clinically significant UTI	1 (0·6%)	0	−0·61% (−1·8 to 0·6)	0·50
Airway or lung†	52 (32%)	35 (21%)	−10·4% (−19·8 to −1·1)	0·0342
CPIS probable‡ pneumonia	34 (21%)	25 (15%)	−5·5% (−13·8 to 2·7)	0·20
CPIS confirmed§ pneumonia	22 (13%)	14 (8%)	−4·9% (−11·6 to 1·2)	0·16
Any major infection¶	27 (16%)	13 (8%)	−8·5% (−15·5 to −1·6)	0·0187

Resultater – fortsat

- Ingen forskelle mellem grupperne mht:
  - Organdysfynktion
  - LOV
  - Anden concomitant behandling
  - Fysisk funktion
  - Performance status

- Ingen signifikante forskelle i a priori definerede subgrupper

Konklusion

Kalorierestriktion v. RFS resulterede i:

- Øget overlevelsestid
- Reduceret mortalitet ved 60 dage
- Reduceret forekomst af større infektion
- Reduceret forekomst af infektion i lunge/luftvej

Ingen forskel i antal dage i live efter udskrivelse fra ITA!

EVIDENS?

REGION