

Recent Advances In Critical Care Nutrition

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Objectives

- 1. Discuss newer data on PN vs EN in critically ill patients**
- 2. Understand the data supporting the use of trophic EN rates in patients with respiratory failure**
- 3. Describe data about the use of Indirect Calorimetry in Estimating Target kcal and protein**

Conflict of Interest Disclosures

- Member of the ASPEN/SCCM Guidelines TaskForce and Author on the Guidelines

Case

- **55 y.o. male COPD with baseline PaCO₂ 55, Type 2 DM, HTN, atrial fibrillation (on coumadin) presents with pneumonia and septic shock. He has new renal failure with creatinine 5.0. Intubated in ED, started on norepinephrine drip, and admitted to MICU. On 70% FiO₂, PEEP 12 and his CXR looks like ARDS.**

Nutrition Questions

- **Should we feed him? How would we assess risk?**
- **How should we feed him?**
 - Enteral vs. Parenteral; Gastric vs. Post-pyloric
- **When should we start feeding him?**
 - Right away vs. few days vs. out of shock
- **What should we feed him?**
 - TF “du jour” vs. special formula
- **How much should we feed him (goals)?**
 - Trophic vs full-calorie
- **What safety measures should we employ?**
 - Gastric residual volume level; GI intolerances

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 - Trophic vs full-calorie; Directed by Indirect Calorimetry
- **What safety measures should we employ?**
 - Gastric residual volume level; GI intolerances

Background

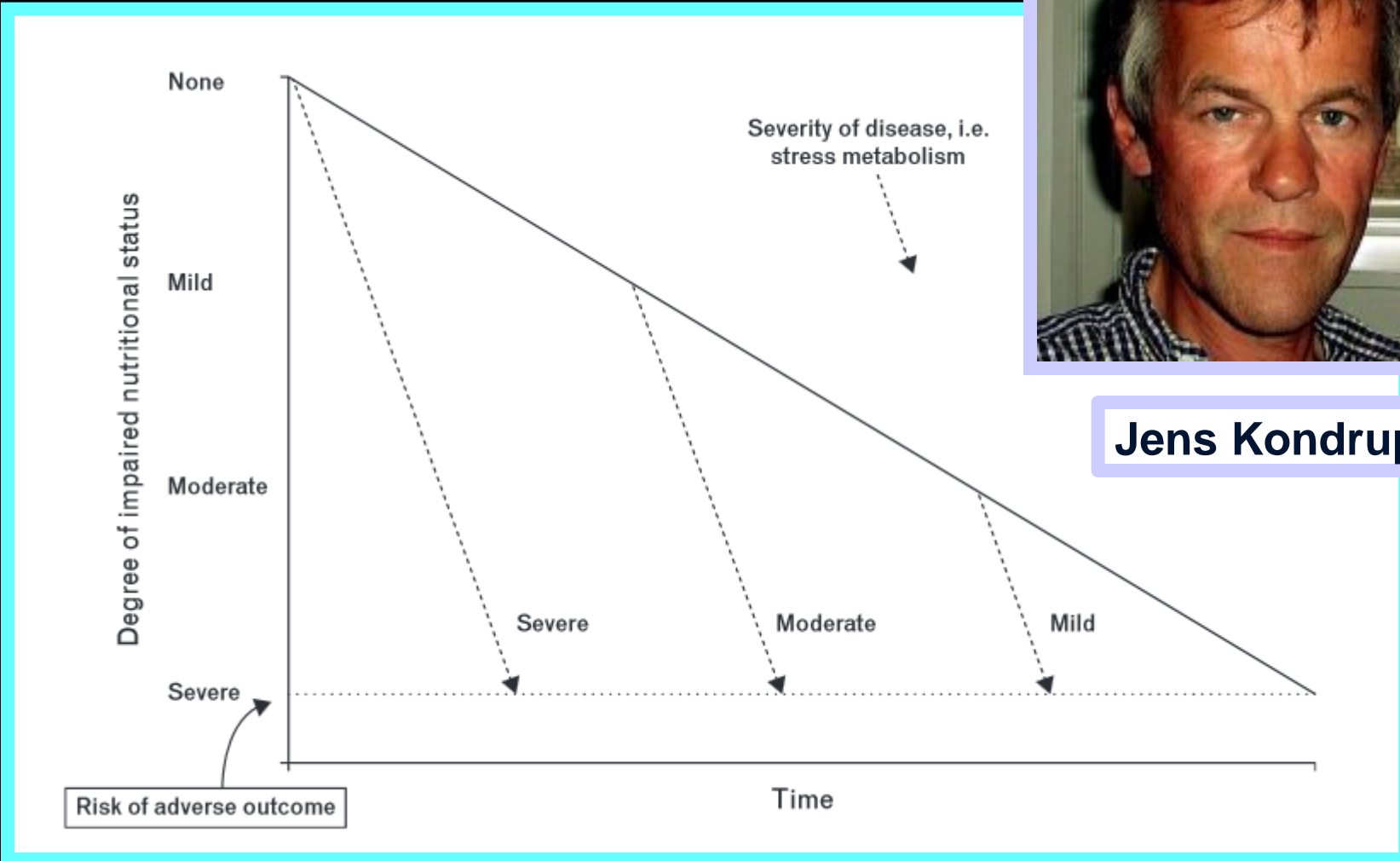
- **Malnutrition in respiratory failure is associated with worse outcomes**
 - Many assume that feeding such patients (even if they are not malnourished) must improve outcomes
- **Consensus statements endorse EN over PN in acute respiratory failure**
- **Strong beliefs about timing, delivery, and composition of EN exist (with emerging data)**

NEW

Concept of Nutritional Risk



Jens Kondrup



Components: Impaired nutrition status and disease severity

J Kondrup (Curr Opin Clin Nutr Metab Care 2014;17:177)



Nutrition Assessment

- **Does Nutrition Risk Assessment identify patients likely to benefit from nutrition therapy?**
 - Very little data on outcomes of nutrition assessment
 - Few studies use formal nutrition assessment as enrollment criteria
 - Recent weight loss
 - Formal assessment scores
- Malnutrition in these patients is hard to define
- Baseline nutrition status versus nutrition risk
- Expert opinion still behind identifying highest risk patients and aggressively providing them with nutritional support

Nutrition Assessment - History

- **Many assessment tools**
 - **Recent weight loss**
 - **Traditional Serum Protein Markers**
 - **Albumin, prealbumin, transferrin, retinol binding protein**
 - **All reflect acute phase response – not reliable**
 - **Anthropomorphic measures**
 - **Skin-fold thickness**
 - **Waist / hip / chest circumference**
 - **Many screening and assessment tools**
 - **Mini Nutritional Assessment (MNA)**
 - **Malnutrition Universal Screening Tool (MUST)**
 - **Short Nutritional Assessment Questionnaire (SNAQ)**
 - **Malnutrition Screening Tool (MST)**
 - **Subjective Global Assessment (SGA)**

Nutrition Assessment – Recent Advances

- **New assessment tools – incorporate disease severity**
 - Nutrition Risk Score (NRS) – 2002 ¹
 - Nutric Score ²
 - High nutritional risk defined as NRS ≥ 5 or Nutric ≥ 6 * ^{2,3}
- **Use of muscle mass**
 - Paraspinous muscles on CT ⁴
 - Ultrasound to determine muscle mass ⁵

1. Kondrup J, et al. *Clin Nutr.* 2003;22:321-336.

2. Heyland DK, et al. *Crit Care.* 2011; 15:R268.

3. Jie B, et al. *Nutrition.* 2012;28(10):1022-1027.

4. Puthuchearry ZA, et al. *JAMA.* 2013;310:1591-1600.

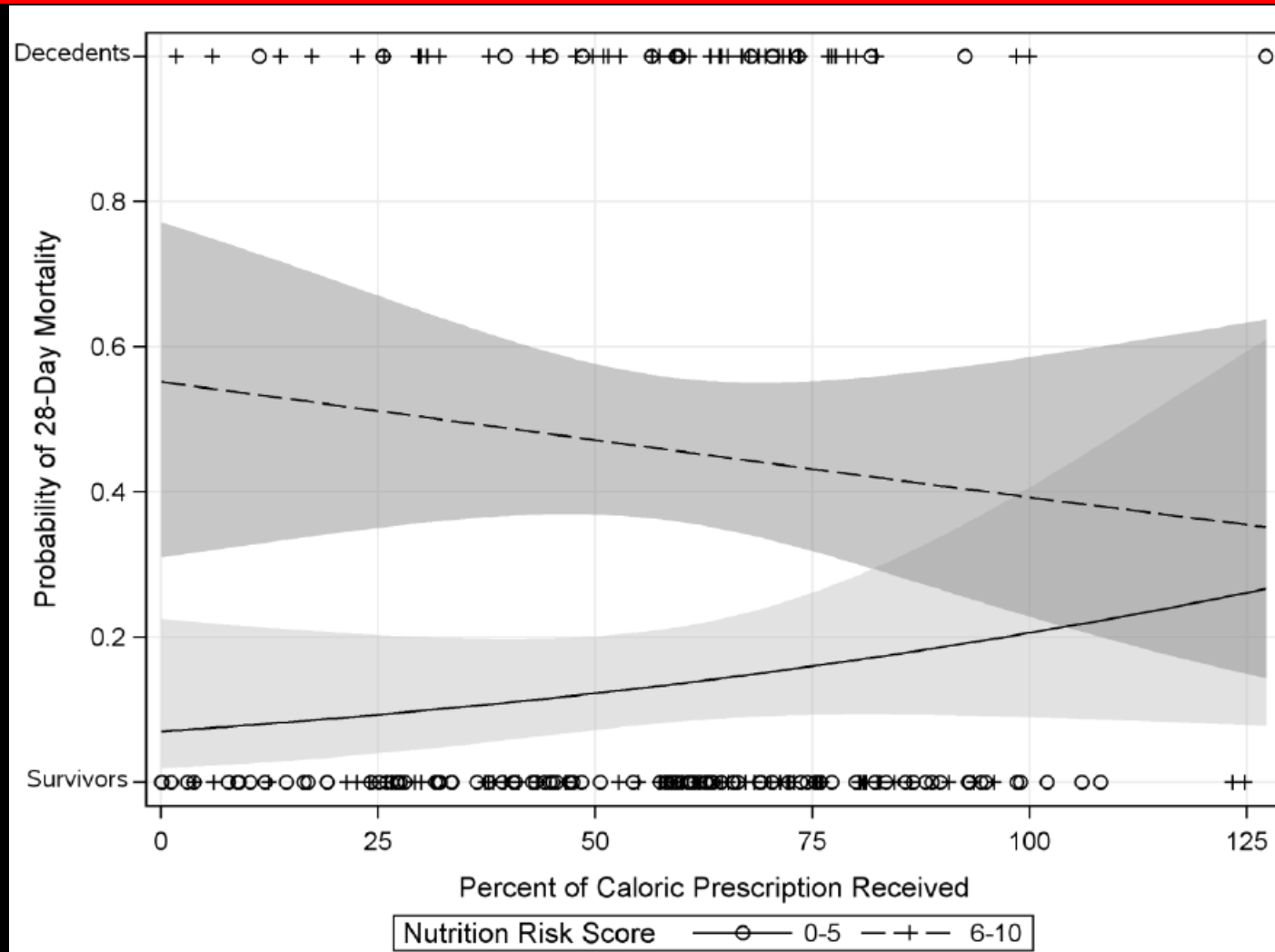
5. Mourtzakis M, et al. *Curr Opin Clin Nutr Metab Care.* 2014;17:389-395.

Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool

Table 4 Proposed nutrition scoring system

Variables in NUTRIC Score	Overall (n = 598)		Random split A (n = 299)		Random split B (n = 299)	
	Range	Points	Range	Points	Range	Points
Age	< 50	0	< 50	0	< 60	0
	50-< 75	1	50-< 75	1	60-< 75	1
	≥75	2	75+	2	75+	2
APACHE II	< 15	0	< 15	0	< 15	0
	15-< 20	1	15-< 19	1	15-< 28	2
	20-28	2	19-28	2	28+	3
	≥28	3	28+	3		
SOFA	< 6	0	< 6	0	< 6	0
	6-< 10	1	6-< 10	1	6-< 10	1
	≥10	2	≥10	2	≥10	2
# Co-morbidities	0-1	0	0, 1	0		0
	2+	1	2, 3	1	1+	1
			4+	2		
Days from hospital to ICU admit	0-< 1	0	0<-1hr	0	ALL	0
	1+	1	1hr	1		
IL6	0-< 400	0	0-350	0	0-< 450	0
	400+	1	350+	1	450+	1
NUTRIC score discriminative performance	In sample		Out of sample		Out of sample	
AUC	0.783		0.771		0.770	
Gen R-Squared	0.169		0.163		0.157	
Gen Max-rescaled R-Squared	0.256		0.246		0.237	

Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool



Heyland DK, et al. *Crit Care*. 2011; 15:R268.

How to Feed the Critically Ill Patient:

EN vs PN

EN vs. PN

- **Is Enteral still better than Parenteral?**
 - Improved TPN solutions
 - Tight glycemic control
 - Improved Central Line Care

Recent Evidence

Early Parenteral Nutrition in Critically Ill Patients With Short-term Relative Contraindications to Early Enteral Nutrition

A Randomized Controlled Trial

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for the Early PN Investigators of the ANZICS Clinical Trials Group

- **ICUs from 31 Austr / NZ Hosp**
- **1372 critically ill adults in first 24 hours of ICU admission**
- **Relative contraindication to early EN & expected ICU > 2 d**
- **45% emerg, 20% elective surg**
- **60% with GI; 20% CV dx**

Early Parenteral Nutrition in Critically Ill Patients With Short-term Relative Contraindications to Early Enteral Nutrition

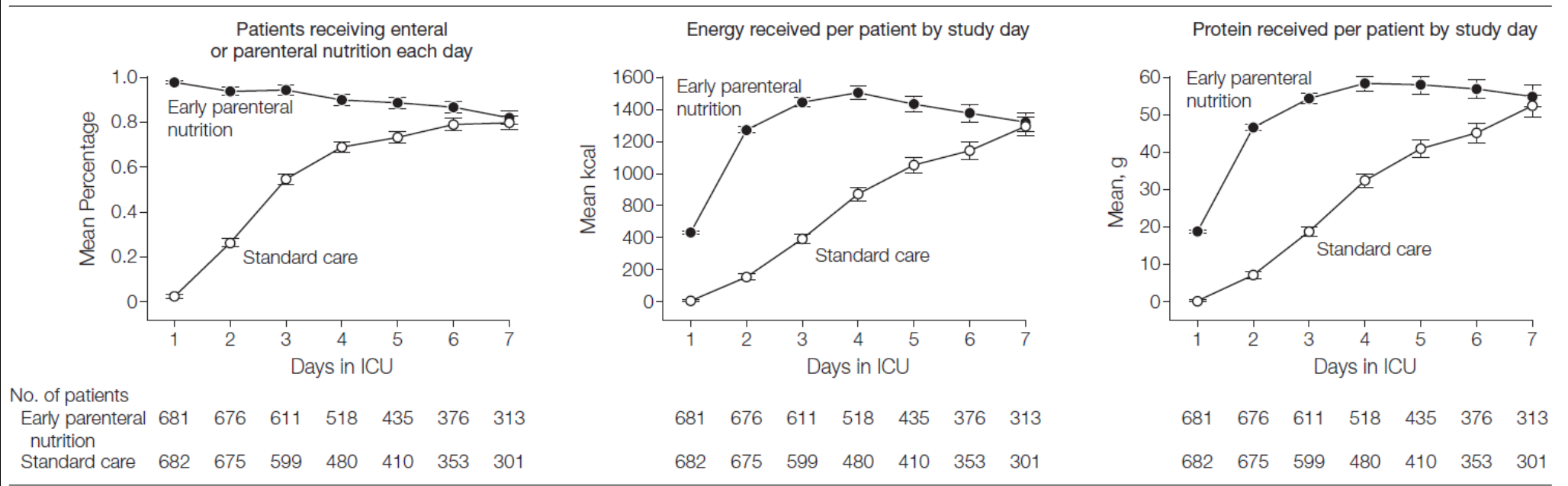
A Randomized Controlled Trial

- **Randomized to SOC vs PN on day 1 targeting goal calories by day 3**
- **In PN group, reminder for EN start on day 3**
- **In SOC group, no protocol; team controlled**
- **Primary Endpoint: 60 day mortality**
- **Other Endpoints: MV; LOS; infections**

Early Parenteral Nutrition in Critically Ill Patients With Short-term Relative Contraindications to Early Enteral Nutrition

A Randomized Controlled Trial

Figure 2. Enteral and Parenteral Nutrition Delivery Process Measures for Patients Remaining in the Study ICU



Early Parenteral Nutrition in Critically Ill Patients With Short-term Relative Contraindications to Early Enteral Nutrition

A Randomized Controlled Trial

Table 2. Mortality, Quality of Life, and Length of Stay

	Standard Care (n = 680) ^a	Early PN (n = 678) ^a	Risk Difference, % (95% CI)	Odds Ratio (95% CI)	P Value
Deaths before study day 60, No. (%)	155 (22.8)	146 (21.5)	-1.26 (-6.6 to 4.1)	0.93 (0.71 to 1.21)	.60
Covariate-adjusted deaths before study day 60 ^b			0.04 (-4.2 to 4.3)	1.00 (0.76 to 1.31)	>.99
Quality of life and physical function, mean (SD) ^c	(n = 525)	(n = 532)	Difference (95% CI)		
RAND-36 general health status ^d	45.5 (26.8) (n = 516)	49.8 (27.6) (n = 525)	4.3 (0.95 to 7.58)		.01
ECOG performance status ^e	1.53 (1.1) (n = 516)	1.51 (1.1) (n = 525)	-0.02 (-0.15 to 0.11)		.70
RAND-36 physical function ^f	40.7 (29.6) (n = 513)	42.5 (30.8) (n = 524)	1.8 (-1.85 to 5.52)		.33
Discharge status and length of stay	(n = 682)	(n = 681)	Difference (95% CI)		
ICU stay, mean (95% CI), d	9.3 (8.9 to 9.7)	8.6 (8.2 to 9.0)	-0.75 (-1.47 to 0.04)		.06
Deaths before ICU discharge, No. (%)	100 (14.66)	81 (11.89)	-2.77% (-8.08% to 2.52%)		.15
Hospital stay, mean (95% CI), d	24.7 (23.7 to 25.8)	25.4 (24.4 to 26.6)	0.7 (-1.4 to 3.1)		.50
Deaths before hospital discharge, No. (%)	151 (22.1)	140 (20.6)	-1.58% (-6.91% to 3.69%)		.51

Early Parenteral Nutrition in Critically Ill Patients With Short-term Relative Contraindications to Early Enteral Nutrition

A Randomized Controlled Trial

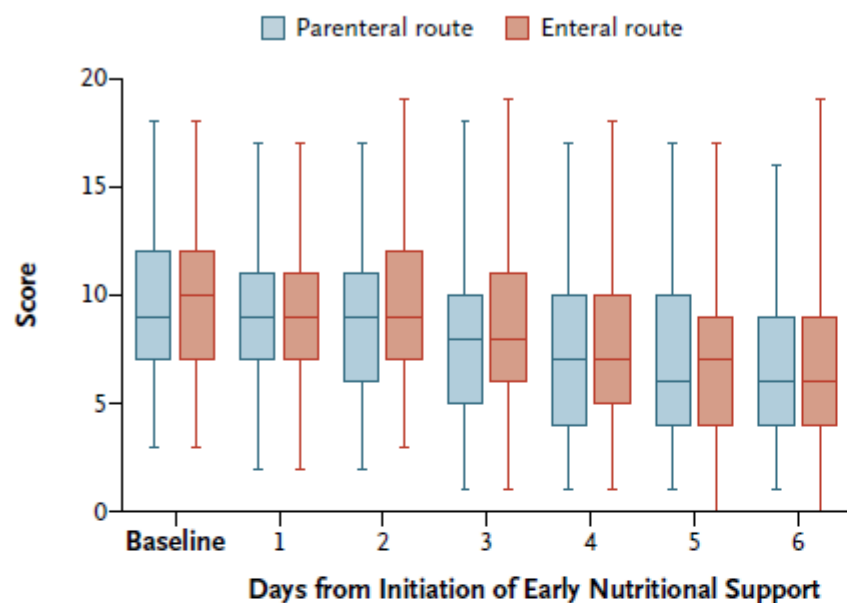
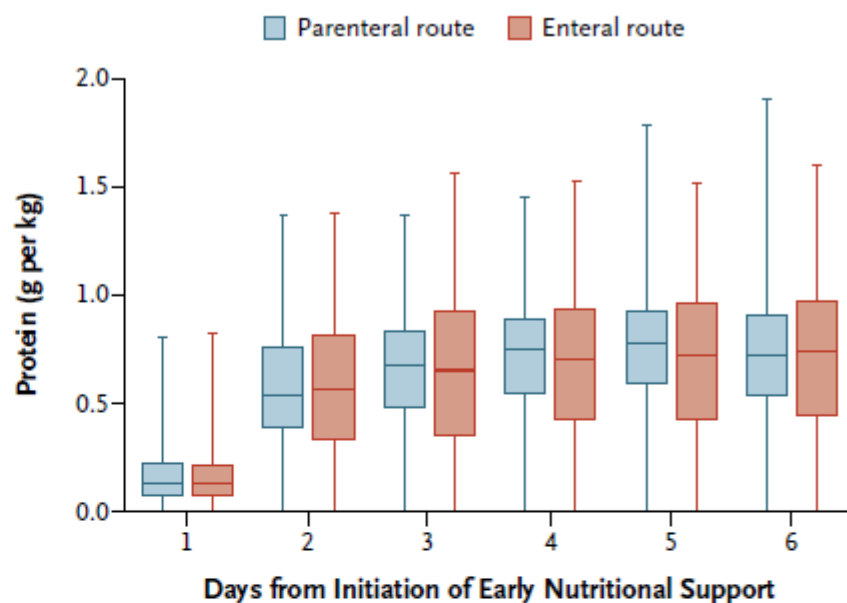
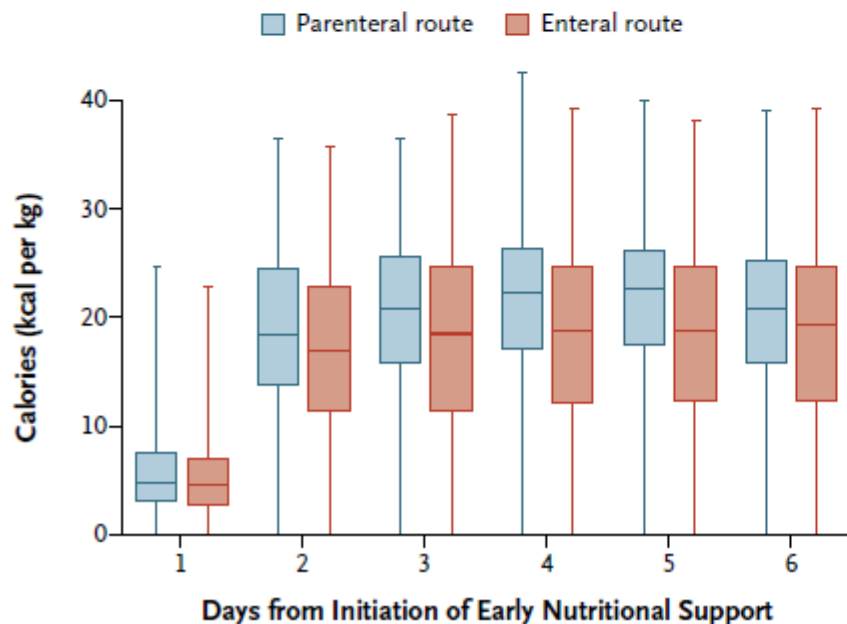
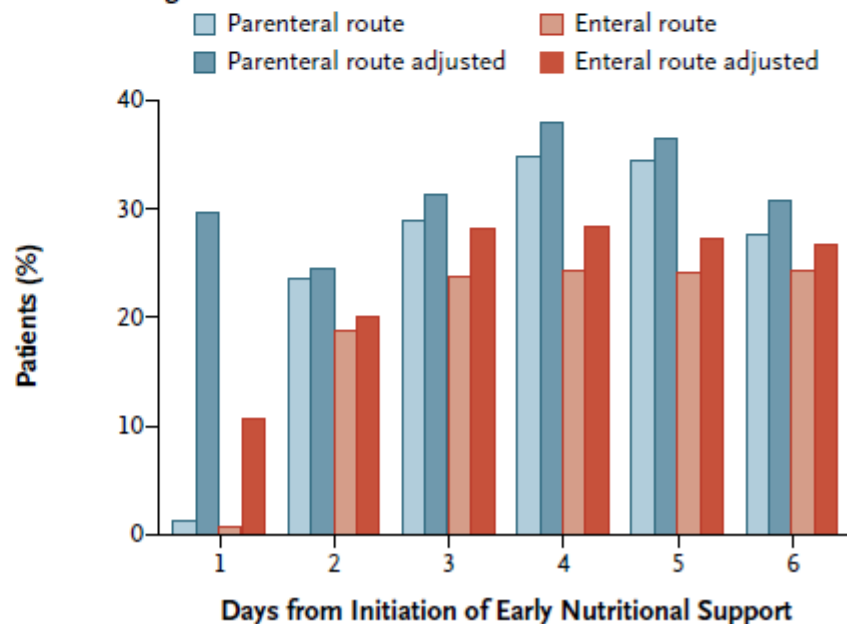
Table 3. Clinically Significant Organ Failure and Concomitant Interventions, Adjusted for Time at Risk (ICU Stay)^a

	Mean (95% CI), Days per 10 Patient × ICU Days		Mean Difference (95% CI), Days per 10 Patient × ICU Days	P Value ^b
	Standard Care (n = 682)	Early PN (n = 681)		
Organ system failures ^c				
Renal	1.66 (1.51 to 1.82)	1.65 (1.51 to 1.81)	−0.01 (−0.28 to 0.33)	.98
Pulmonary	8.51 (8.34 to 8.69)	8.54 (8.37 to 8.71)	0.03 (−0.31 to 0.37)	.88
Hepatic	1.14 (1.09 to 1.20)	1.08 (1.03 to 1.14)	−0.06 (−0.16 to 0.06)	.15
Coagulation	2.23 (2.09 to 2.38)	1.89 (1.78 to 2.02)	−0.34 (−0.57 to −0.08)	.01
Cardiovascular	1.16 (1.05 to 1.27)	0.99 (0.89 to 1.09)	−0.17 (−0.34 to 0.04)	.11
MODs	4.04 (3.85 to 4.25)	3.93 (3.74 to 4.13)	−0.11 (−0.48 to 0.29)	.59
No. of organ failures ^d	1.47 (1.44 to 1.51)	1.42 (1.39 to 1.46)	−0.05 (−0.12 to 0.02)	.12
Concomitant therapies and tertiary outcomes				
Renal replacement therapy	0.99 (0.82 to 1.81)	0.80 (0.67 to 0.96)	−0.19 (−0.42 to 0.16)	.25
Invasive mechanical ventilation	7.73 (7.55 to 7.92)	7.26 (7.09 to 7.44)	−0.47 (−0.82 to −0.11)	.01
Pressure ulcer treatment ^e	0.87 (0.74 to 1.02)	0.78 (0.67 to 0.92)	−0.09 (−0.30 to 0.22)	.54
Low serum albumin (<2.5 g/dL)	5.47 (5.28 to 5.67)	5.76 (5.56 to 5.97)	0.29 (−0.10 to 0.71)	.15
Systemic antibiotic use	7.95 (7.78 to 8.12)	8.05 (7.88 to 8.22)	0.10 (−0.23 to 0.45)	.55
Witnessed aspiration ^f	1.59 (0.98 to 2.54)	1.96 (1.21 to 3.13)	0.37 (−0.80 to 3.45)	.66
With new pulmonary infiltrates ^f	0.48 (0.20 to 1.15)	0.71 (0.30 to 1.72)	0.23 (−0.36 to 0.37)	.65

Trial of the Route of Early Nutritional Support in Critically Ill Adults

- **2400 pts in UK ICUs; mixed med-surg**
- **Randomized to EN vs PN – started w/in 36 hrs**
- **Continued randomized treatment for 5 days**
- **Primary outcome: All-cause 30-d mortality**

- **Age: 63; 14% surgical**
- **APACHE II: 19.6; SOFA: 9.5; 83% ventilated**

A SOFA Score**B Protein Intake****C Caloric Intake****D Caloric Target Met**

Trial of the Route of Early Nutritional Support in Critically Ill Adults

Table 3. Primary and Secondary Outcomes.*

Outcome	Parenteral Group (N=1191)	Enteral Group (N=1197)	Absolute Difference between Groups (95% CI)	Relative Risk (95% CI)	P Value
Primary outcome: death within 30 days — no./total no. (%)	393/1188 (33.1)	409/1195 (34.2)	1.15 (–2.65 to 4.94) [†]	0.97 (0.86 to 1.08) [‡]	0.57 [§]
Secondary outcomes					
No. of days alive and free of specified organ support up to 30 days [¶]					
Free of advanced respiratory support	14.3±12.1	14.3±12.2	0.04 (–0.94 to 1.01)		0.94
Free of advanced cardiovascular support	18.9±13.5	18.5±13.6	0.41 (–0.63 to 1.53)		0.44
Free of renal support	19.1±13.9	18.8±14.0	0.26 (–0.85 to 1.47)		0.66
Free of neurologic support	19.2±13.8	18.9±14.0	0.34 (–0.81 to 1.36)		0.57
Free of gastrointestinal support	13.0±11.7	13.2±11.8	–0.12 (–1.05 to 0.80)		0.81
No. of treated infectious complications per patient	0.22±0.60	0.21±0.56	0.01 (–0.04 to 0.06)		0.72

Trial of the Route of Early Nutritional Support in Critically Ill Adults

No. of treated infectious complications per patient	0.22±0.60	0.21±0.56	0.01 (-0.04 to 0.06)	0.72
Noninfectious complications — no./total no. (%)				
Episodes of hypoglycemia	44/1191 (3.7)**	74/1197 (6.2)††	2.49 (0.75 to 4.22)†	0.006§
Elevated liver enzymes	212/1191 (17.8)	179/1197 (15.0)	-2.85 (-5.81 to 0.12)†	0.07§
Nausea requiring treatment	44/1191 (3.7)	53/1197 (4.4)	0.73 (-0.85 to 2.32)†	0.41§
Abdominal distention	78/1191 (6.5)	99/1197 (8.3)	1.72 (-0.38 to 3.82)†	0.12§
Vomiting	100/1191 (8.4)	194/1197 (16.2)	7.81 (5.20 to 10.43)†	<0.001§
New or substantially worsened pressure ulcers	181/1190 (15.2)	179/1195 (15.0)	-0.23 (-3.10 to 2.64)†	0.91§
Median no. of days in the ICU (IQR)‡‡	8.1 (4.0–15.8)	7.3 (3.9–14.3)		0.15
Median no. of days in acute care hospital (IQR)§§	17 (8–34)	16 (8–33)		0.32

Harvey SE, et al. *N Engl J Med.* 2014;371(18):1673-84.

Doig and Calories: Summary

- TPN did not improve 60-d mortality in critically ill patients with contraindication to early EN ²
- Early TPN in this group may have reduced time on ventilator slightly (? 1 day / 20 ICU days)
- But no difference in LOS, infections

- Initial TPN for 5 days had similar outcomes (and delivery) to EN
- TPN had less hypoglycemia and vomiting

1. Doig, et al. *JAMA*. 2013; 309(20):2130-8.

2. Harvey SE, et al. *N Engl J Med*. 2014;371(18):1673-84.

EN vs. PN Meta-analysis: ICU Patients - Mortality

Study or Subgroup	EN		PN		Weight	Risk Ratio		Year	Risk Ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI			
A Caloric intake PN > EN										
Rapp	9	18	3	20	4.2%	3.33	[1.07, 10.43]	1983		
Young	10	28	10	23	10.3%	0.82	[0.42, 1.62]	1987		
Kudsk	1	51	1	45	0.8%	0.88	[0.06, 13.70]	1992		
Woodcock	9	17	5	21	6.6%	2.22	[0.92, 5.40]	2001		
Subtotal (95% CI)		114		109	21.8%	1.58	[0.75, 3.35]			

Total events

29

19

Heterogeneity: $\tau^2 = 0.27$; $\text{Chi}^2 = 5.81$, $\text{df} = 3$ ($P = 0.12$); $I^2 = 48\%$

Test for overall effect: $Z = 1.20$ ($P = 0.23$)

RR 1.58; (0.75, 3.35)

B Caloric intake PN ~ EN

Adams	1	23	3	23	1.2%	0.33	[0.04, 2.97]	1986		
Dunham	1	12	1	15	0.8%	1.25	[0.09, 17.98]	1994		
Borzotta	5	28	1	21	1.3%	3.75	[0.47, 29.75]	1994		
Hadfield	2	13	6	11	2.9%	0.28	[0.07, 1.13]	1995		
Kalfarentzos	1	18	2	20	1.1%	0.56	[0.05, 5.62]	1997		
Cerra	7	31	8	35	6.5%	0.99	[0.40, 2.41]	1998		
Casas	0	11	2	11	0.7%	0.20	[0.01, 3.74]	2007		
Justo Meirelles	1	12	1	10	0.8%	0.83	[0.06, 11.70]	2011		
Harvey	450	1186	431	1185	50.0%	1.04	[0.94, 1.16]	2014		
Subtotal (95% CI)		1334		1331	65.3%	1.03	[0.93, 1.14]			

Total events

468

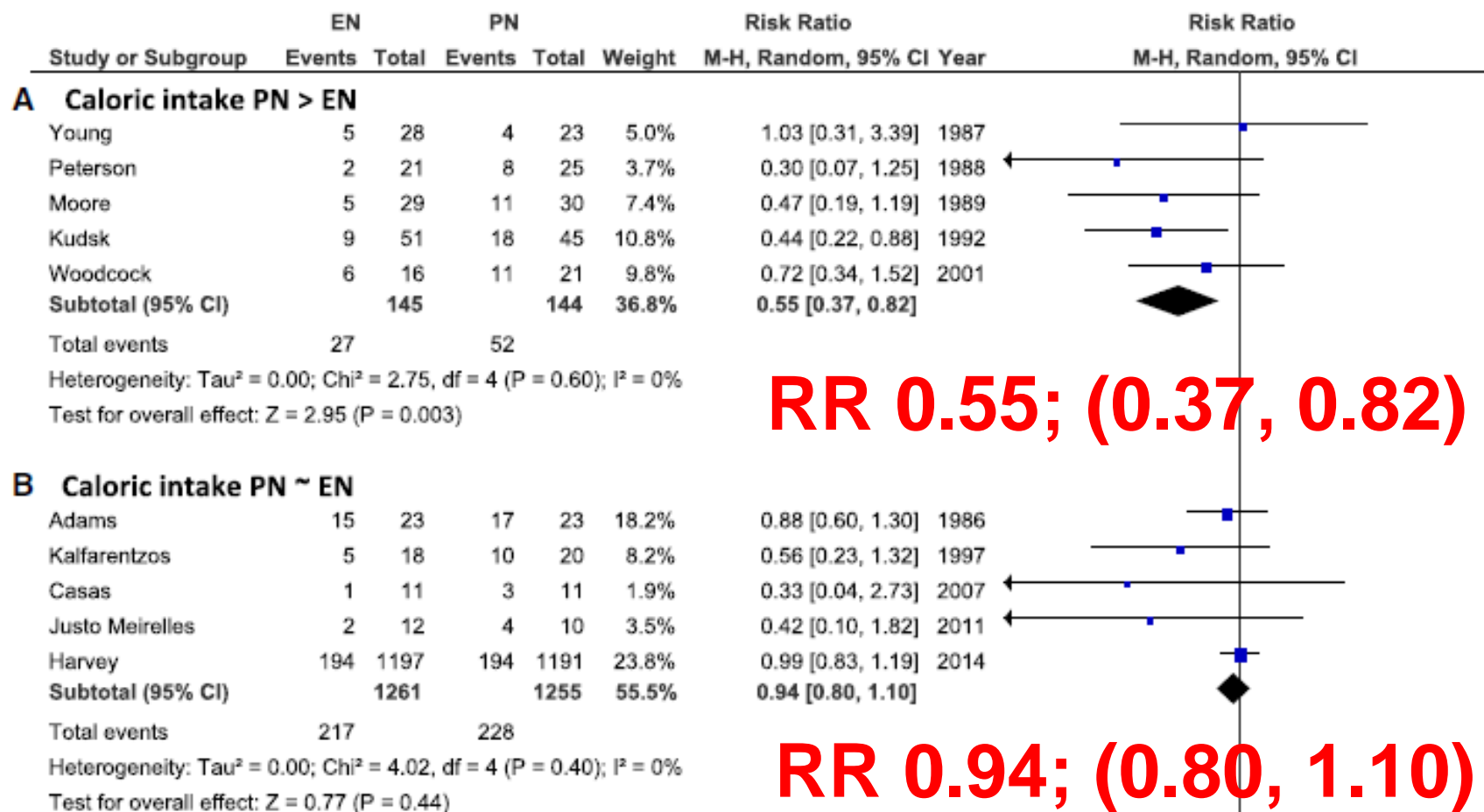
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Heterogeneity: $\tau^2 = 0.00$; $\text{Chi}^2 = 7.47$, $\text{df} = 8$ ($P = 0.49$); $I^2 = 0\%$

Test for overall effect: $Z = 0.60$ ($P = 0.55$)

RR 1.03; (0.93, 1.14)

EN vs. PN Meta-analysis: ICU Infectious Complications



RR 0.55; (0.37, 0.82)

RR 0.94; (0.80, 1.10)

Supplementing EN with PN

- Using parenteral nutrition to supplement enteral nutrition to increase caloric delivery
- Slowly taper off PN as tolerance of EN increases
- Society Guidelines differ:
 - ESPEN – start suppl PN w/in 2 days ¹
 - Canadian / ASPEN – start EN ASAP but wait to start suppl PN ^{2,3}

1. Singer P, et al. *Clin Nutr.* 2009;28:387-400

2. Heyland DK, et al. *JPEN.* 2003;27:355-73.

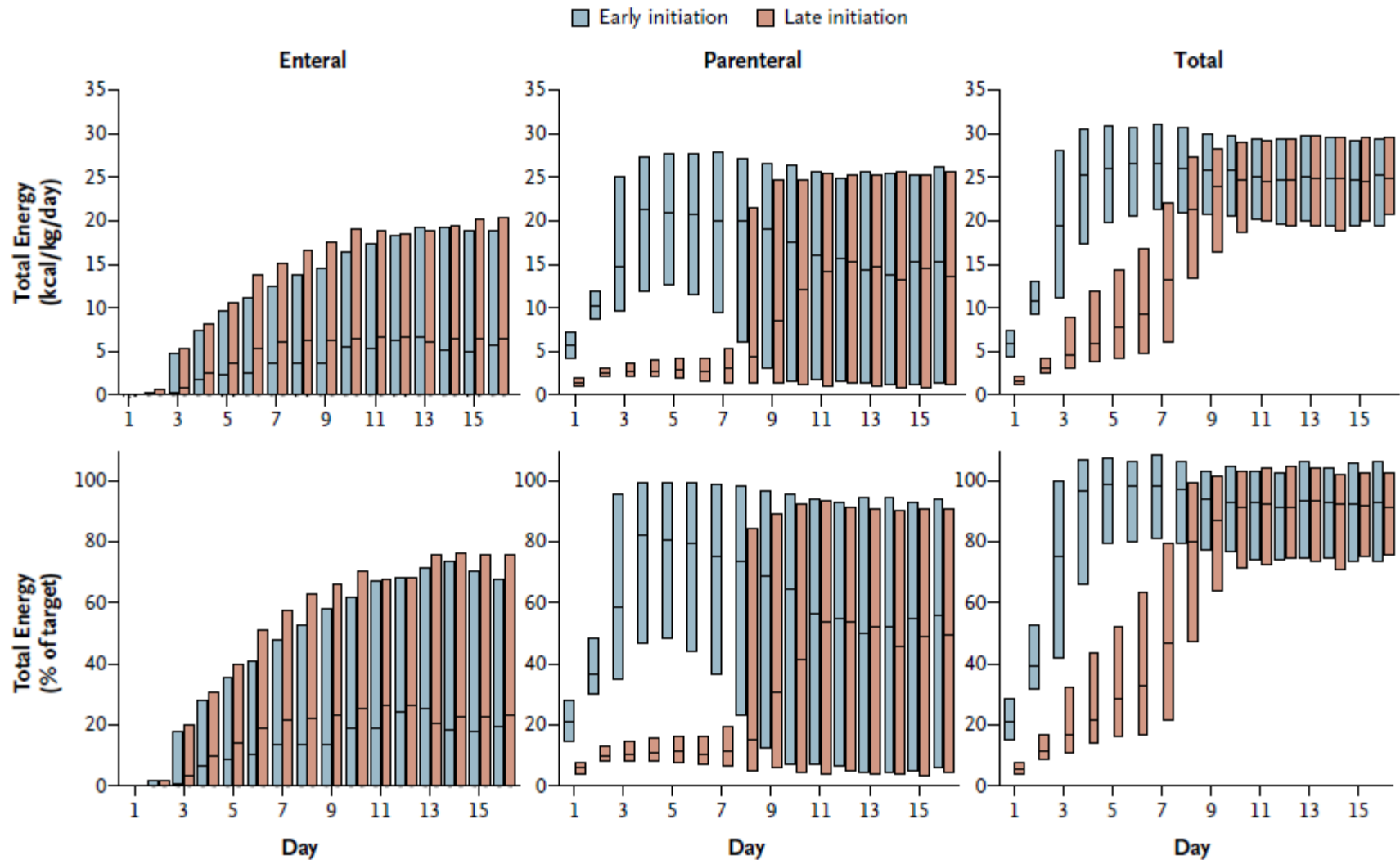
3. Taylor BE, et al. *Crit Care Med.* 2016;44:390-438.

ORIGINAL ARTICLE

Early versus Late Parenteral Nutrition in Critically Ill Adults

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EPaNIC: Early vs. Late TPN



No. in ICU

Late initiation	2328	1399	913	655	436	313	2328	1399	913	655	436	313	2328	1399	913	655	436	313
Early initiation	2312	1438	975	736	517	371	2312	1438	975	736	517	371	2312	1438	975	736	517	371

EPaNIC: Early vs. Late TPN

Table 2. Outcomes.*

Variable	Late-Initiation Group (N=2328)	Early-Initiation Group (N=2312)	P Value
Safety outcome			
Vital status — no. (%)			
Discharged live from ICU within 8 days	1750 (75.2)	1658 (71.7)	0.007
Death			
In ICU	141 (6.1)	146 (6.3)	0.76
In hospital	242 (10.4)	251 (10.9)	0.63
Within 90 days after enrollment†	257 (11.2)	255 (11.2)	1.00
Nutrition-related complication — no. (%)			
Hypoglycemia during intervention — no. (%)‡	81 (3.5)	45 (1.9)	0.001
Primary outcome			
Duration of stay in ICU§			
Median (interquartile range) — days	3 (2–7)	4 (2–9)	0.02
Duration >3 days — no. (%)	1117 (48.0)	1185 (51.3)	0.02

EPaNIC: Early vs. Late TPN

Secondary outcome			
New infection — no. (%)			
Any	531 (22.8)	605 (26.2)	0.008
Airway or lung	381 (16.4)	447 (19.3)	0.009
Bloodstream	142 (6.1)	174 (7.5)	0.05
Wound	64 (2.7)	98 (4.2)	0.006
Urinary tract	60 (2.6)	72 (3.1)	0.28
Mechanical ventilation			
Median duration (interquartile range) — days	2 (1–5)	2 (1–5)	0.02
Duration >2 days — no. (%)	846 (36.3)	930 (40.2)	0.006
Hazard ratio (95% CI) for time to definitive weaning from ventilation	1.06 (0.99–1.12)		0.07
Duration of hospital stay			
Median (interquartile range) — days	14 (9–27)	16 (9–29)	0.004
Duration >15 days — no. (%)	1060 (45.5)	1159 (50.1)	0.001
Hazard ratio (95% CI) for time to discharge alive from hospital	1.06 (1.00–1.13)		0.04

Role of Disease and Macronutrient Dose in the Randomized Controlled EPaNIC Trial

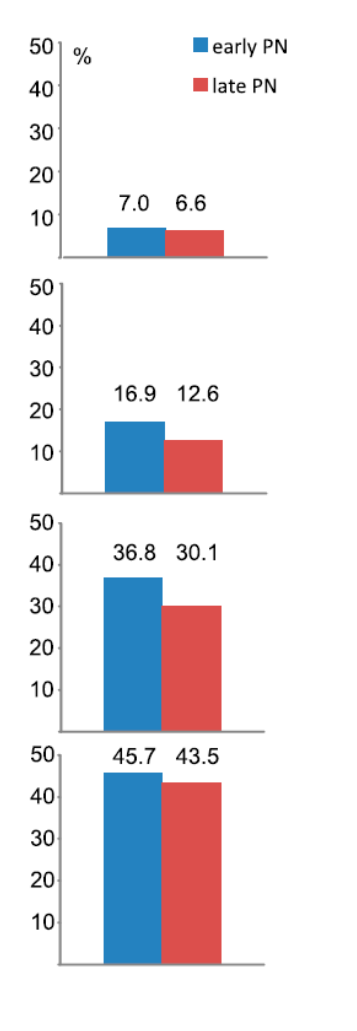
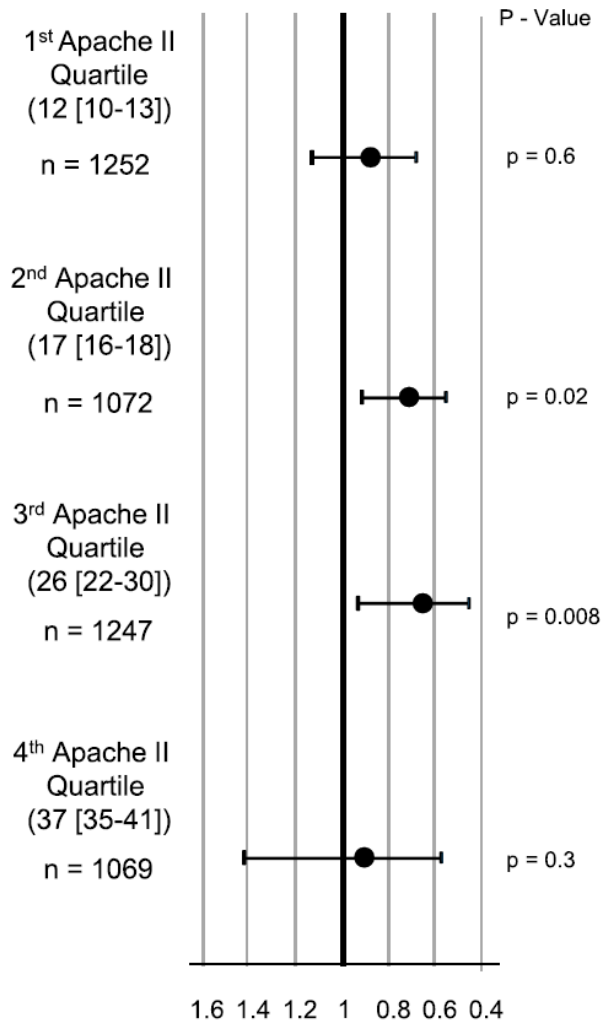
A Post Hoc Analysis

Michael P. Casaer^{1,2}, Alexander Wilmer³, Greet Hermans^{2,3}, Pieter J. Wouters^{1,2}, Dieter Mesotten^{1,2}, and Greet Van den Berghe^{1,2}

- **Post hoc analysis of EPaNIC trial**
- **Looked at mortality and infections between early vs late PN in pt subgroups**
 - **APACHE II Quartiles**
 - **Excluding cardiac surgery patients**
- **Overall Kcal and Glucose vs. protein as kcal**
 - **Complex statistics to look at kcal to days 3,5, & 7**

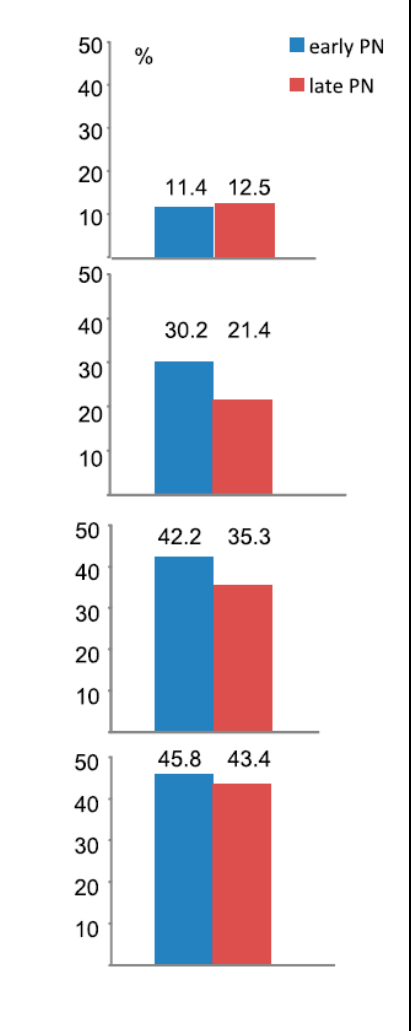
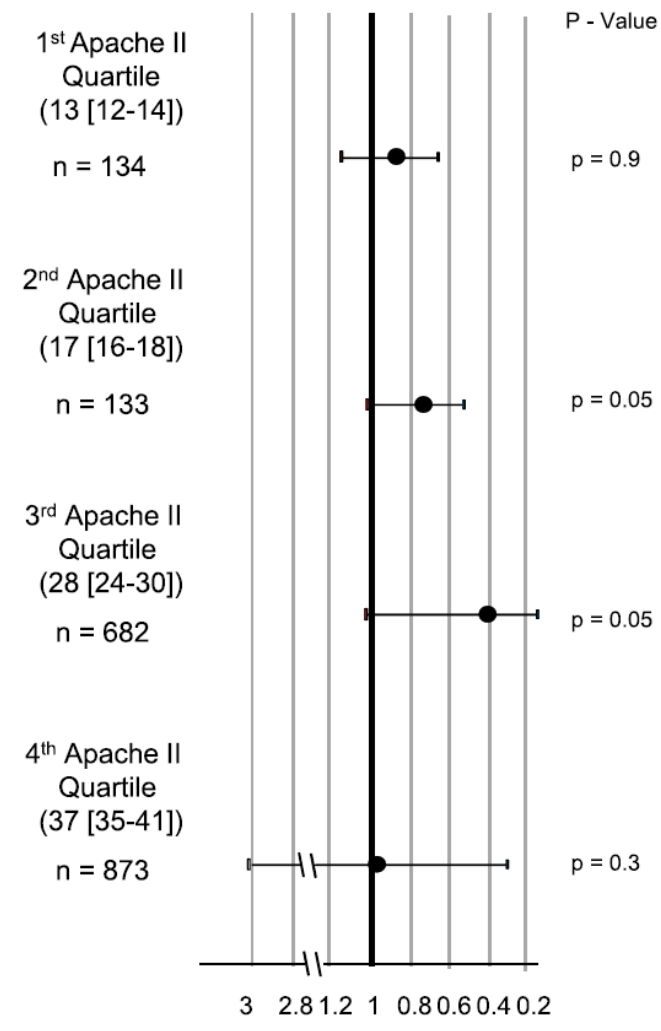
Casaer MP, et al. *AJRCCM*. 2013; 187:247-55.

C **Total Population**
(N = 4640)



In favor of early PN In favor of late PN
OR for acquisition of a new infection

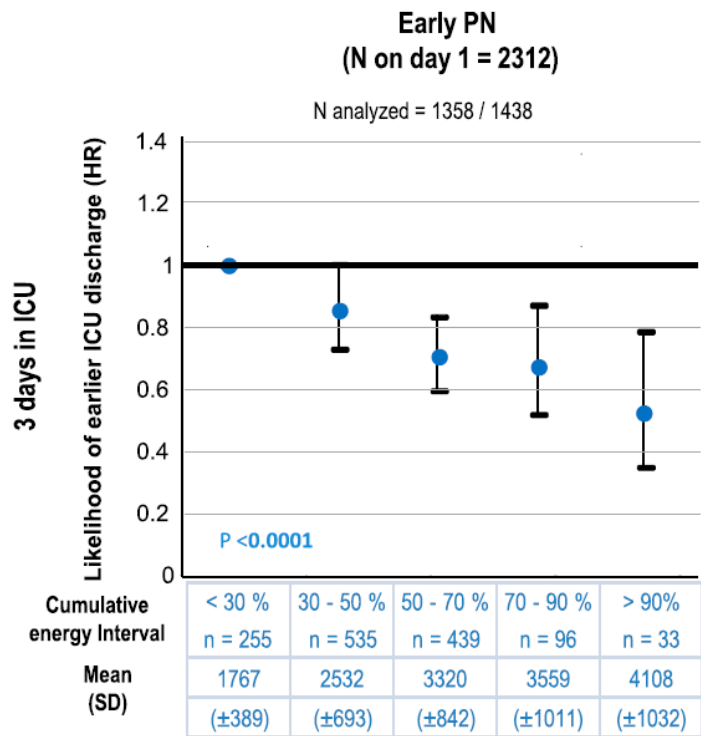
D **Other patients**
(N = 1822)



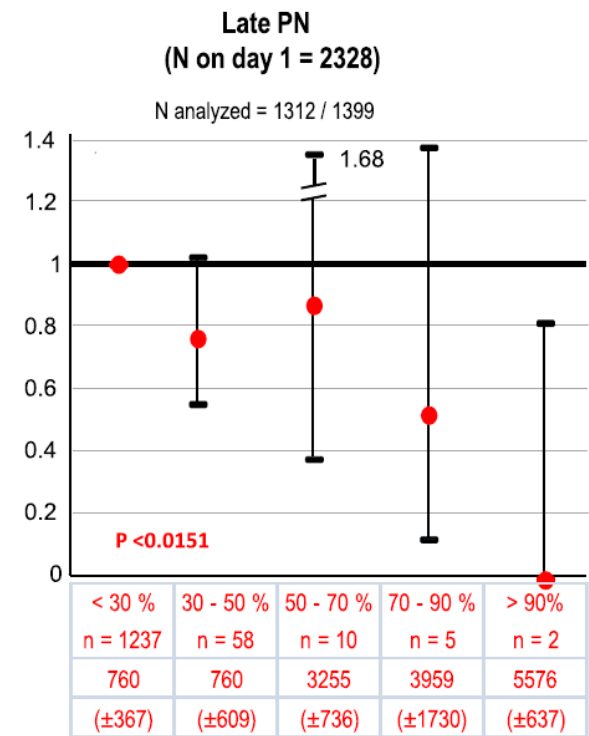
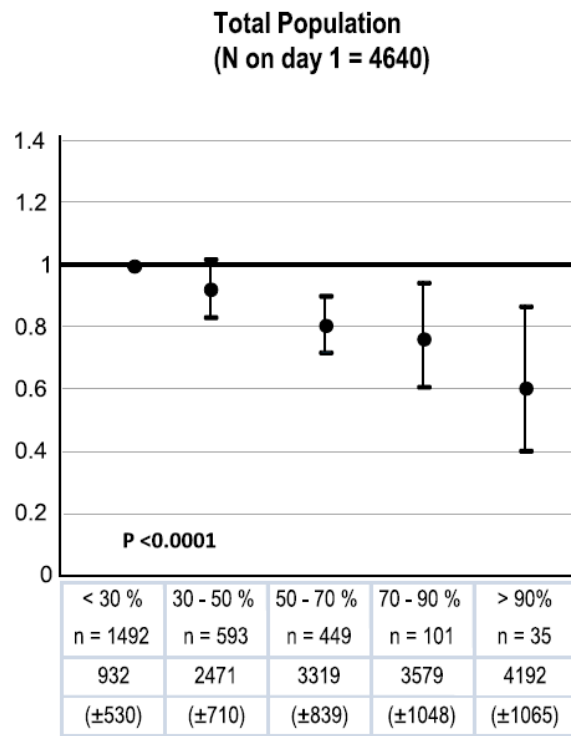
In favor of early PN In favor of late PN
OR for acquisition of a new infection

Patients acquiring a new infection during ICU stay

EPaNIC Post hoc: Overall Kcal and Alive ICU Discharge



N analyzed = 893 / 975



N analyzed = 823/ 913

Summary of Early PN in Critical Illness

- **A little bit of conflicting results**
- **No real benefit demonstrated in clinical outcomes**
- **Although study of early supplemental PN demonstrated harm, overall PN is probably safe**
- **No real data on PN in malnourished patients or subsets of critical illnesses**

**How much should we feed
patients?
(especially early in critical illness)**

Quantity of Feeds

- **Limited data suggest initiating EN w/in 24 hrs is beneficial (esp trauma)**
- **But those data don't address quantity of enteral feeding**
- **If we start enteral feeds within 24-48 hours, do we have to get to target or goal rates as soon as possible?**

“Trophic” Feeds

- **The minimum amount of enteral nutrition required for the mucosal benefits is unknown**
- **As little as 10-40% of caloric requirements preserves mucosal structure in dogs¹ and pigs²**
- **Trophic= nourishment or growth**
 - **Low volume continuous feeds for the purpose of nourishing the intestinal mucosa**

1. Owens L, et al. *J of Nutrition*. 2002;132:2717-22.

2. Burrin DG, et al. *Am J Clin Nutr*. 2000;71:16

EN Benefits: Achieved at Different Doses?

- **Non-Nutrition benefits - Lower dose, needed in all patients**

Gastrointestinal responses

Gut integrity

Gut/lung axis of inflamm

Motility/contractility

Absorptive capacity

Commensal bacteria

Secretory IgA, GALT tissue

Trophic effect epithelium

Reduced bact virulence

Immune responses

Modulate regulatory cells

Stimulate oral tolerance

Duod colon receptors

Promote Th-2 >Th-1 lymphocytes

Maintain MALT tissue

Modulate adhesion molecules

Metabolic responses

Incretin to insulin sens

Attenuate stress metab

Reduce hyperglycemia (AGES)

Enhance fuel utilization

- **Nutrition benefits – Higher dose, needed in high risk patients**

Protein, calories

Maintain LBM

Micronutrients, anti-oxidants

Stimulate protein synthesis

Initial Trophic vs Full Enteral Feeding in Patients With Acute Lung Injury

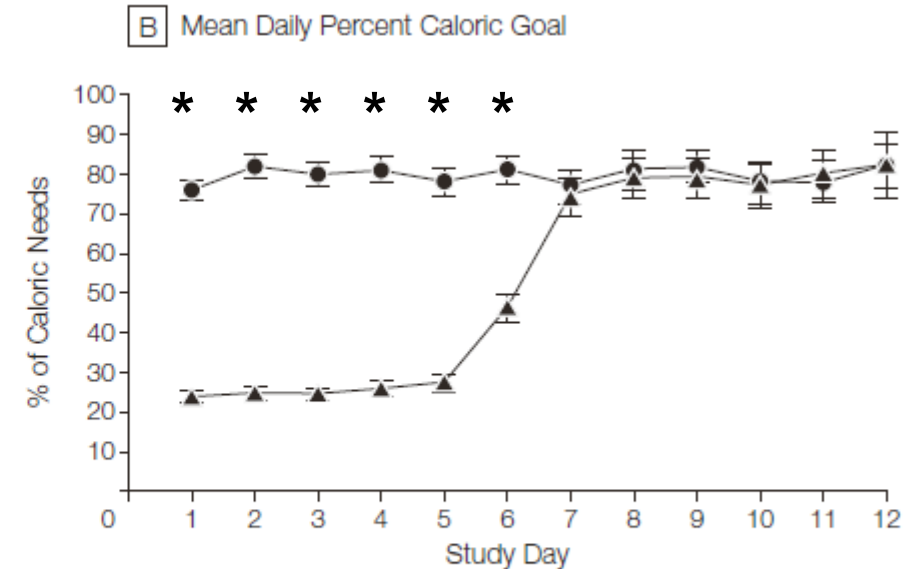
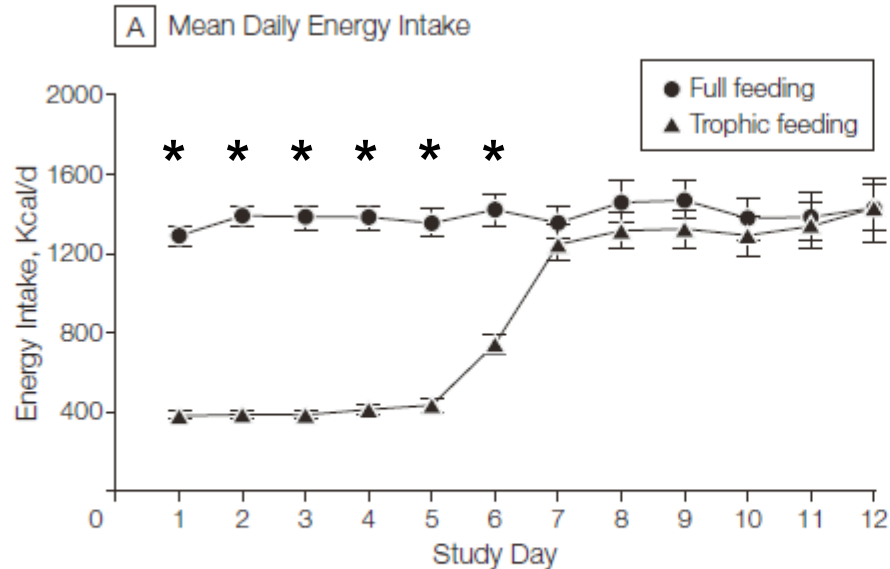
The EDEN Randomized Trial

The National Heart, Lung, and Blood
Institute Acute Respiratory Distress
Syndrome (ARDS) Clinical Trials
Network*

- **1000 mech vent patients with ALI**
 - Mostly Medical – Pneumonia (65%); Sepsis (15%)
 - 38% on vasopressors at enrollment
 - GRV threshold 400 cc
- **Factorial design with n-3 fatty acid / placebo**
- **Trophic (N=508) vs. Goal (N=492) for first 6d**
- **Primary endpoint: Ventilator-free days**

EDEN: Enteral Feeds Delivered

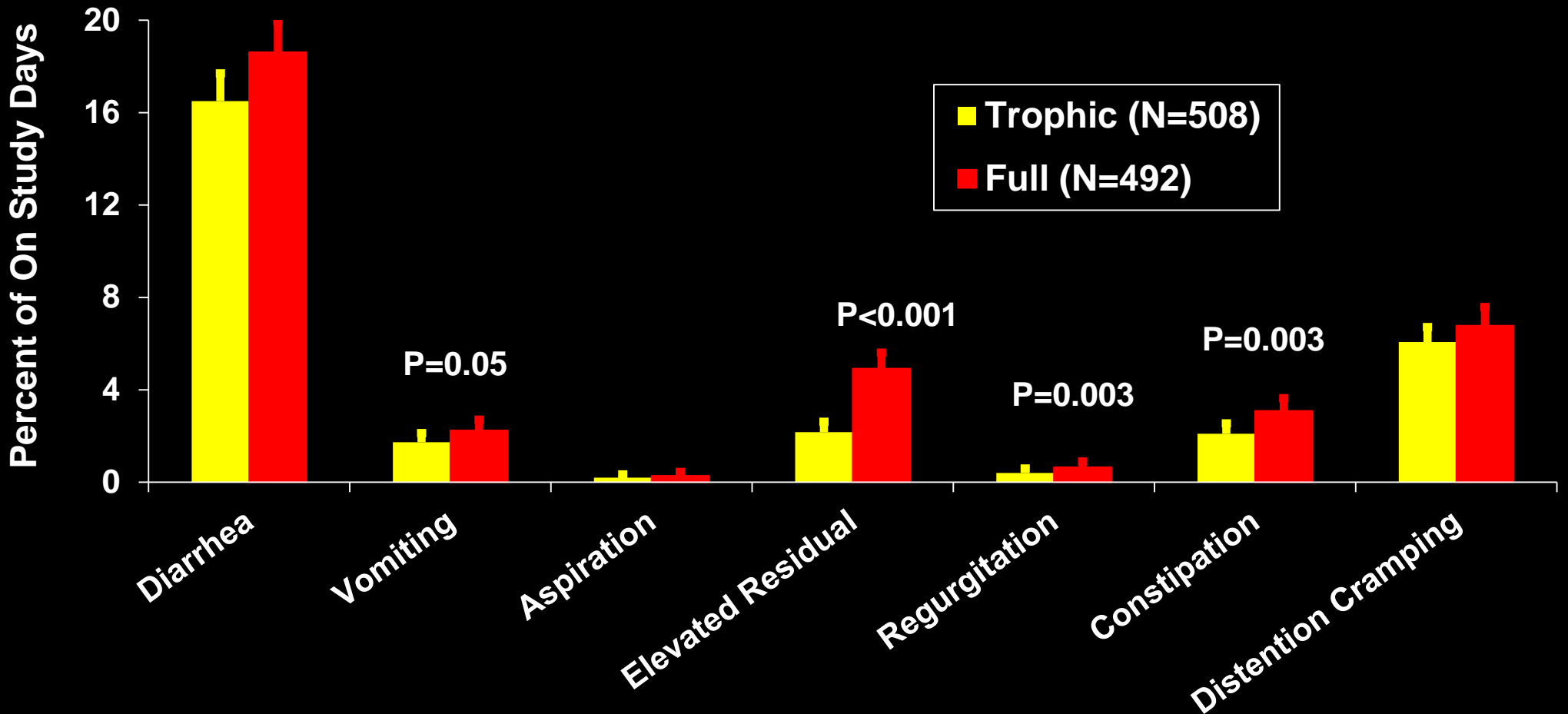
Figure 4



No. of patients	1	2	3	4	5	6	7	8	9	10	11	12
Full feeding	467	419	379	334	295	251	216	186	162	147	123	109
Trophic feeding	482	426	373	323	286	237	196	166	154	140	122	109

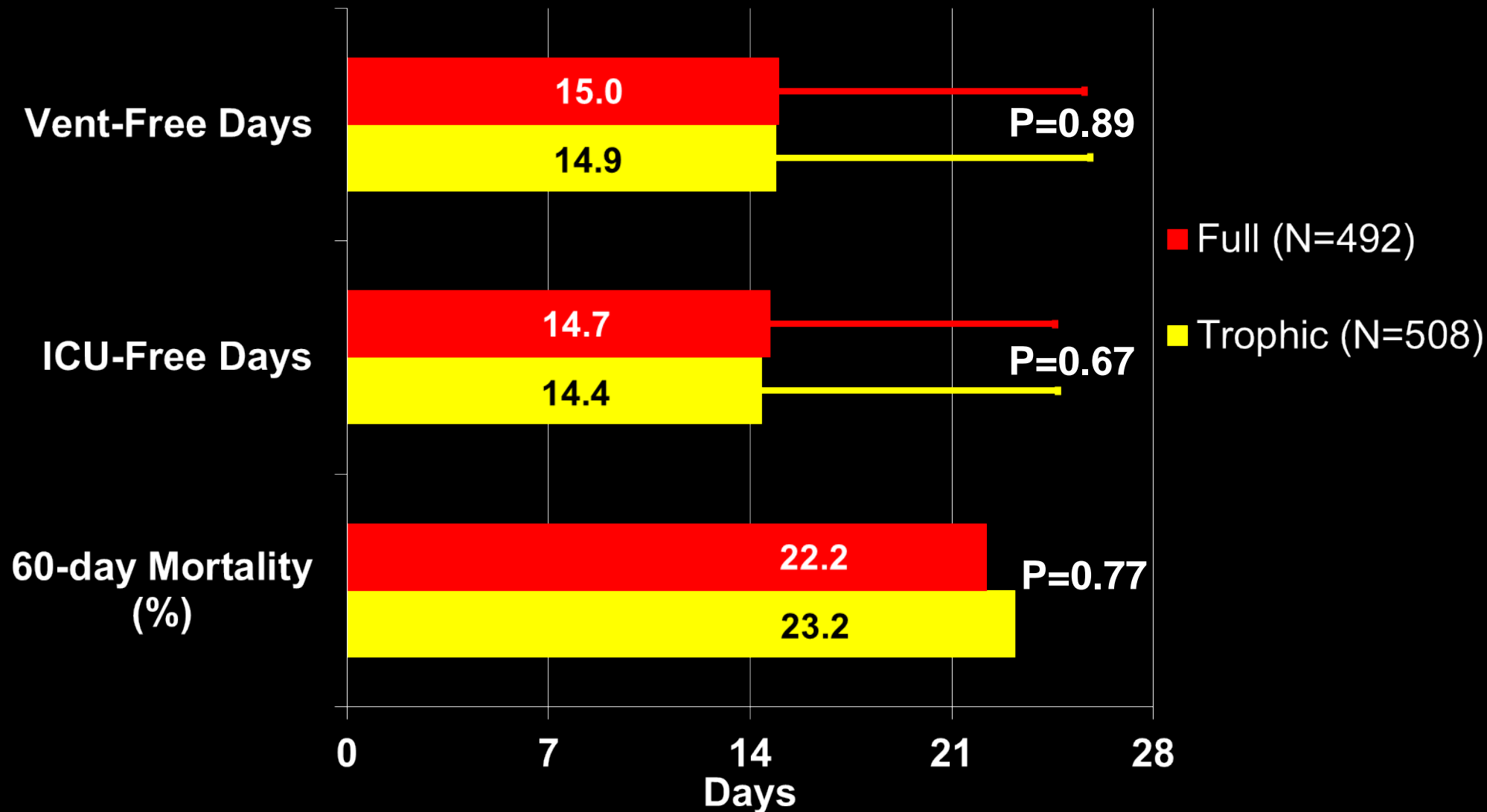
No. of patients	1	2	3	4	5	6	7	8	9	10	11	12
Full feeding	471	426	385	335	295	251	218	188	163	148	124	108
Trophic feeding	489	434	377	332	291	242	203	174	159	143	128	115

EDEN: Percent of Feeding Days with Specific GI Intolerances



eFig 1: NHLBI ARDS Network. *JAMA*. 2012; 307(8):795.

EDEN: Outcomes



NHLBI ARDS Network. *JAMA*. 2012; 307(8):795.

Optimal Initial Amount of Enteral Feeding in Critically Ill Patients: Systematic Review and Meta-Analysis

- **Meta-analysis of adult ICU patients**
- **Initial trophic vs full feeding**
- **4 RCTs (N=1540 participants total)**
- **Primary analyses: Mortality**

Optimal Initial Amount of Enteral Feeding in Critically Ill Patients: Systematic Review and Meta-Analysis

- **No diff in Mortality (OR 0.95; 0.74-1.20; P=0.65)**
- **Subgroup analysis:**
 - **Trophic >33% of goal: OR 0.61 (0.39-0.97; P=0.04)**
- **No difference in Hospital or ICU LOS**
- **Serious GI Intolerance: 23% trophic vs 31% full (OR 0.66; 0.39-1.12; P=0.12)**

Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults

- **894 critically ill patients**
 - 7 hospitals in Saudi Arabia and Canada
 - 75% medical, 21% non-op trauma
 - 96% MV, 55% on pressors
- **Randomized, open label trial**
- **40-60% goal cal + protein vs 70-100% goal kcal for up to 14 days**
- **Primary Endpoint: 90 day mortality**

Arabi YM, et al. *NEJM*. 2015;372(25):2398-2408.

Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults

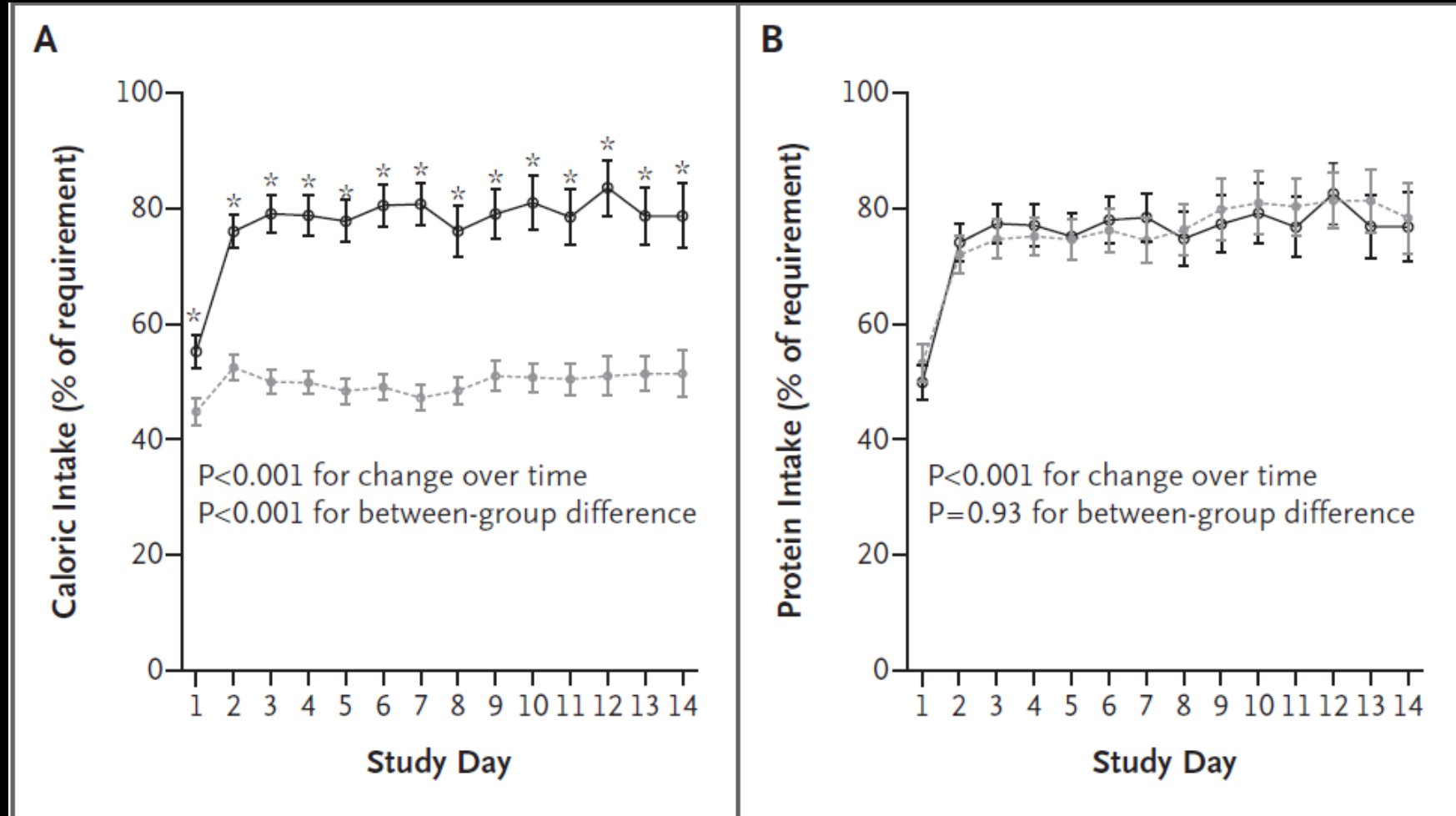
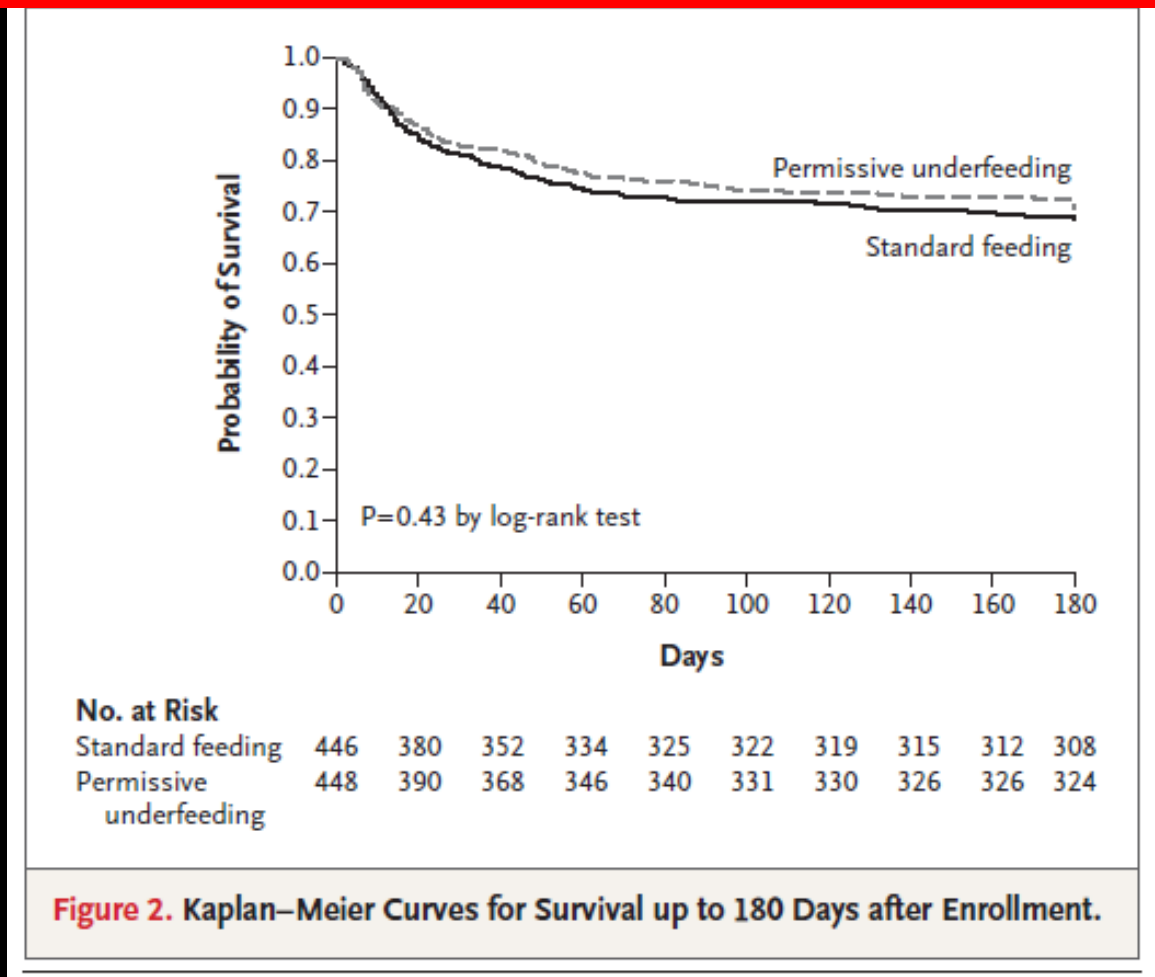


Table 3. Outcomes in the Permissive-Underfeeding and Standard-Feeding Groups.*

Outcome	Permissive Underfeeding (N = 448)	Standard Feeding (N = 446)	Relative Risk (95% CI)	P Value
Death by 90 days — no./total no. (%)	121/445 (27.2)	127/440 (28.9)	0.94 (0.76–1.16)	0.58
Death in the ICU — no. (%)	72 (16.1)	85 (19.1)	0.84 (0.63–1.12)	0.24
Death by 28 days — no./total no. (%)	93/447 (20.8)	97/444 (21.8)	0.95 (0.74–1.23)	0.7
Death in the hospital — no./total no. (%)	108/447 (24.2)	123/445 (27.6)	0.87 (0.70–1.09)	0.24
Death by 180 days — no./total no. (%)	131/438 (29.9)	140/436 (32.1)	0.93 (0.76–1.14)	0.48
Duration of mechanical ventilation — days				
Median	9	10		0.49†
Interquartile range	5–15	5–16		
Days free from mechanical ventilation				
Median	77	75		0.48†
Interquartile range	0–84	0–84		
ICU length of stay — days				
Median	13	13		0.46†
Interquartile range	8–21	8–20		
ICU-free days				
Median	72	71		0.28†
Interquartile range	0–81	0–79		
Hospital length of stay — days				
Median	28	30		0.24†
Interquartile range	15–54	14–63		
Incident renal-replacement therapy — no./total no. (%)	29/406 (7.1)	45/396 (11.4)	0.63 (0.40–0.98)	0.04

Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults

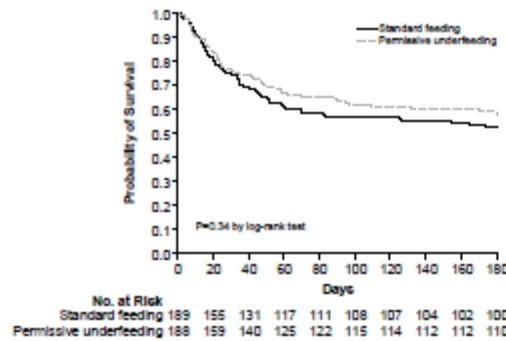


Arabi YM, et al. *NEJM*. 2015;372(25):2398-2408.

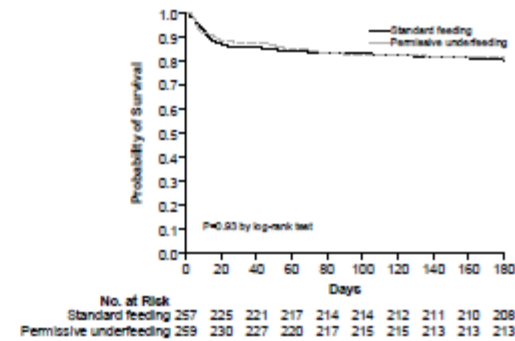
Permissive Underfeeding or Standard Enteral Feeding in High and Low Nutritional Risk Critically Ill Adults: Post-hoc Analysis of the PermiT trial

Yaseen M Arabi MD¹, Abdulaziz S Aldawood MD¹, Hasan M Al-Dorzi MD¹, Hani M Tamim MPH, PhD^{1,2}, Samir H Haddad MD¹, Gwynne Jones MD³, Lauralyn McIntyre MD MSc³, Othman Solaiman MD⁴, Maram H Sakkijha RD¹, Musharaf Sadat MBBS¹, Shihab Mundekadan RN¹, Anand Kumar MD⁵, Sean. M Bagshaw MD MSc⁶, Sangeeta Mehta MD⁷ and the PermiT trial group

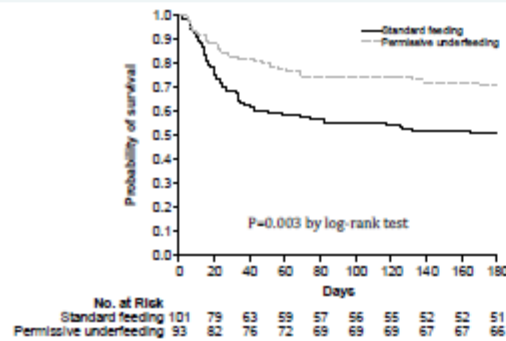
NUTRIC score 5-9



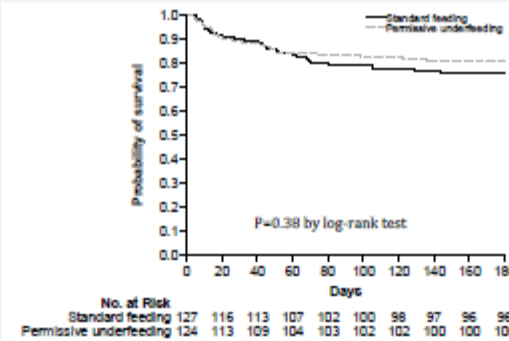
NUTRIC score 0-4



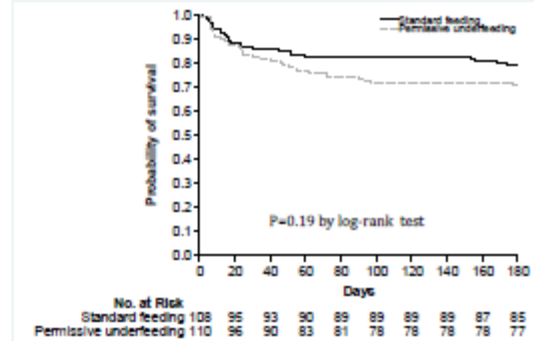
Prealbumin ≤ 0.10 g/L



Prealbumin > 0.10 and ≤ 0.15 g/L



Prealbumin > 0.15 g/L



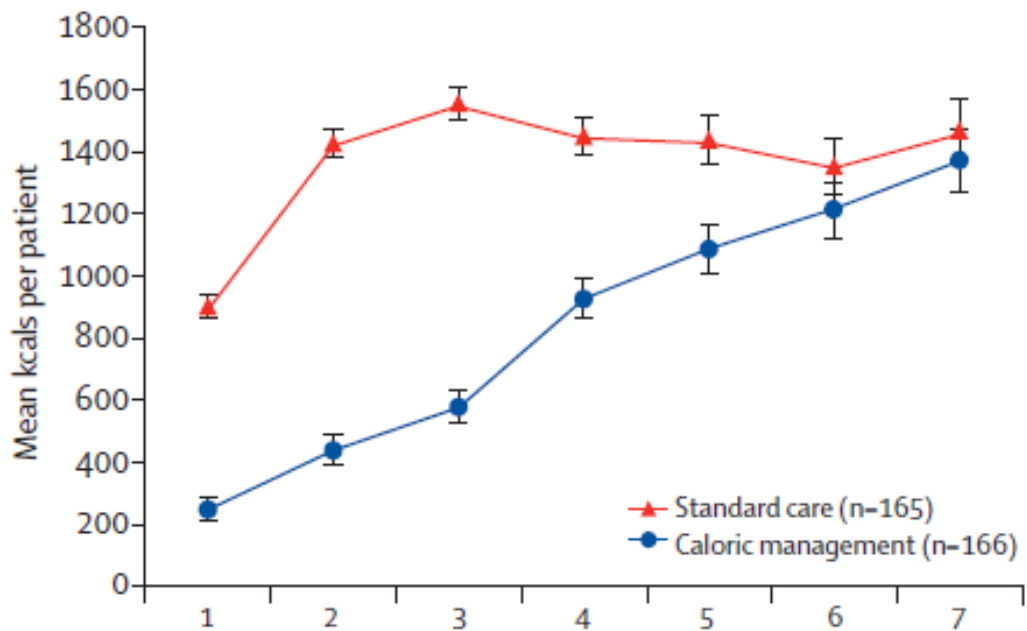
Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial

- **339 pts from 13 ICUs in Australia / New Zealand**
- **Refeeding syndrome = low phos by day 3 of EN**
- **RCT, single blind – std vs restricted calories**
 - **Std: Continue advance to full EN with phos repletion**
 - **Restricted: 20 kcal/hr until phos repleted (≥ 2 days)**
- **1^o outcome: Days alive outside of ICU**
- **65% Medical; APACHE II 18; 91% ventilated**

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

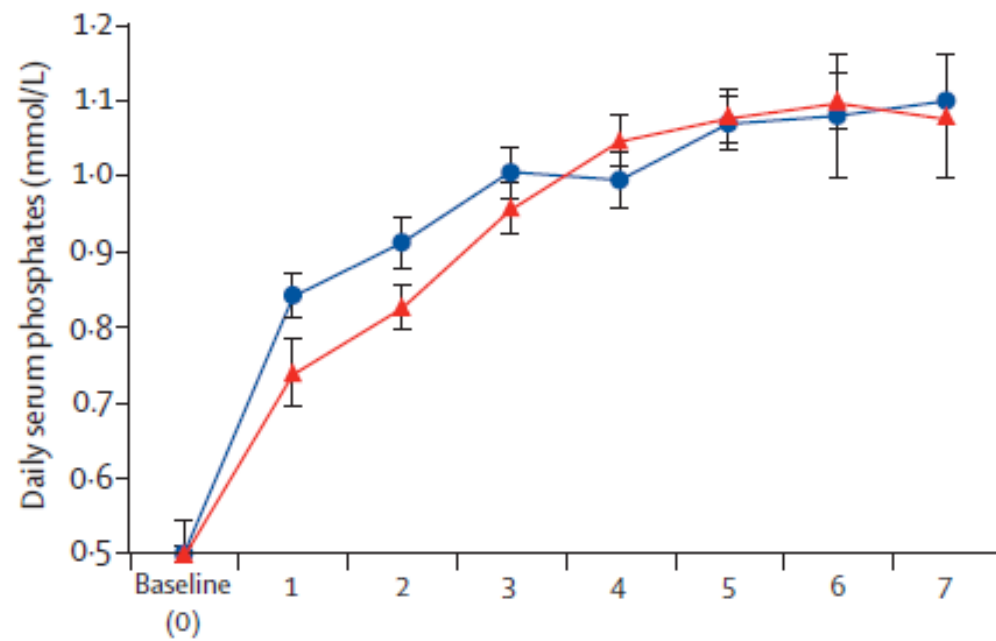
Study process measures

A Mean caloric intake per study day

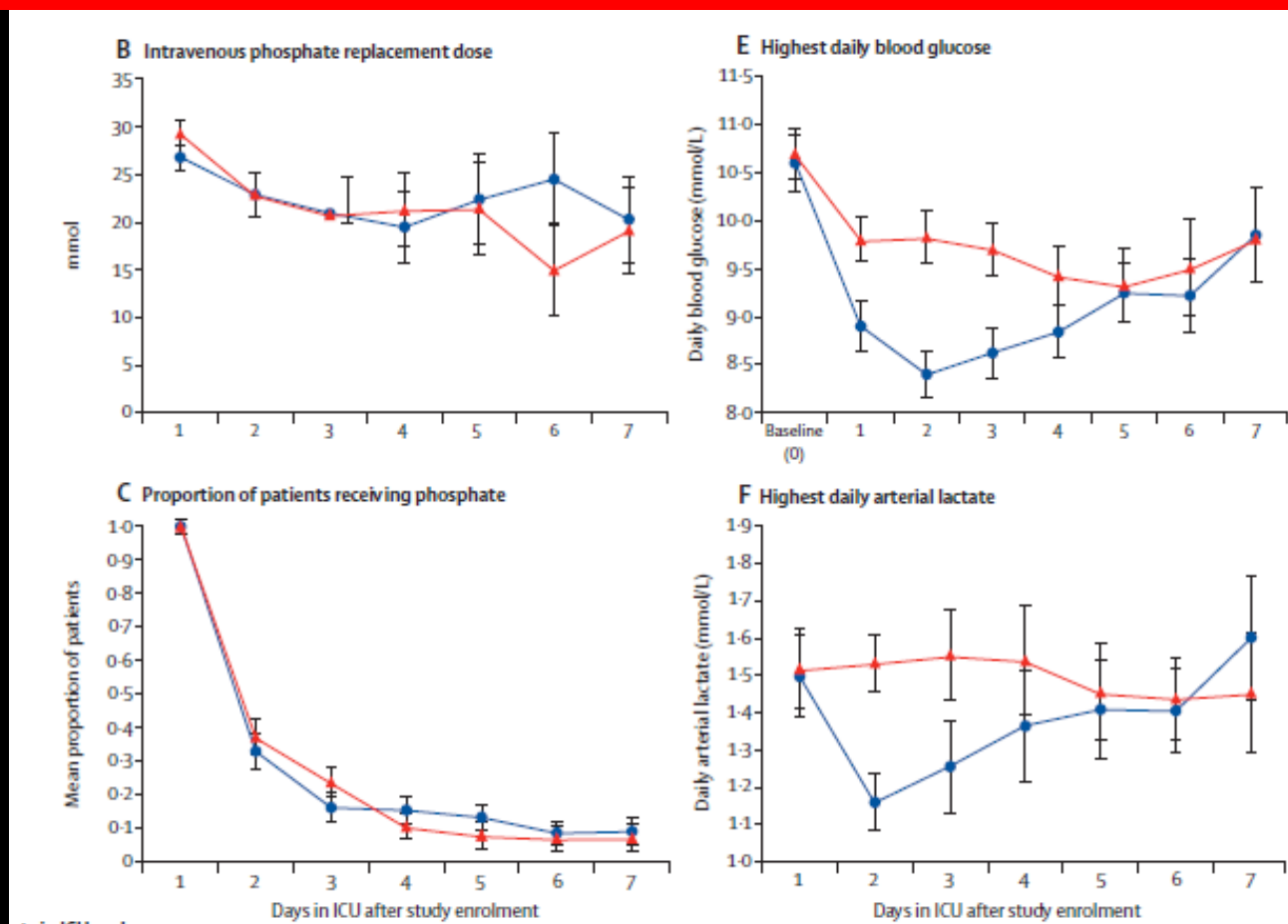


Physiological response

D Lowest daily serum phosphates



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



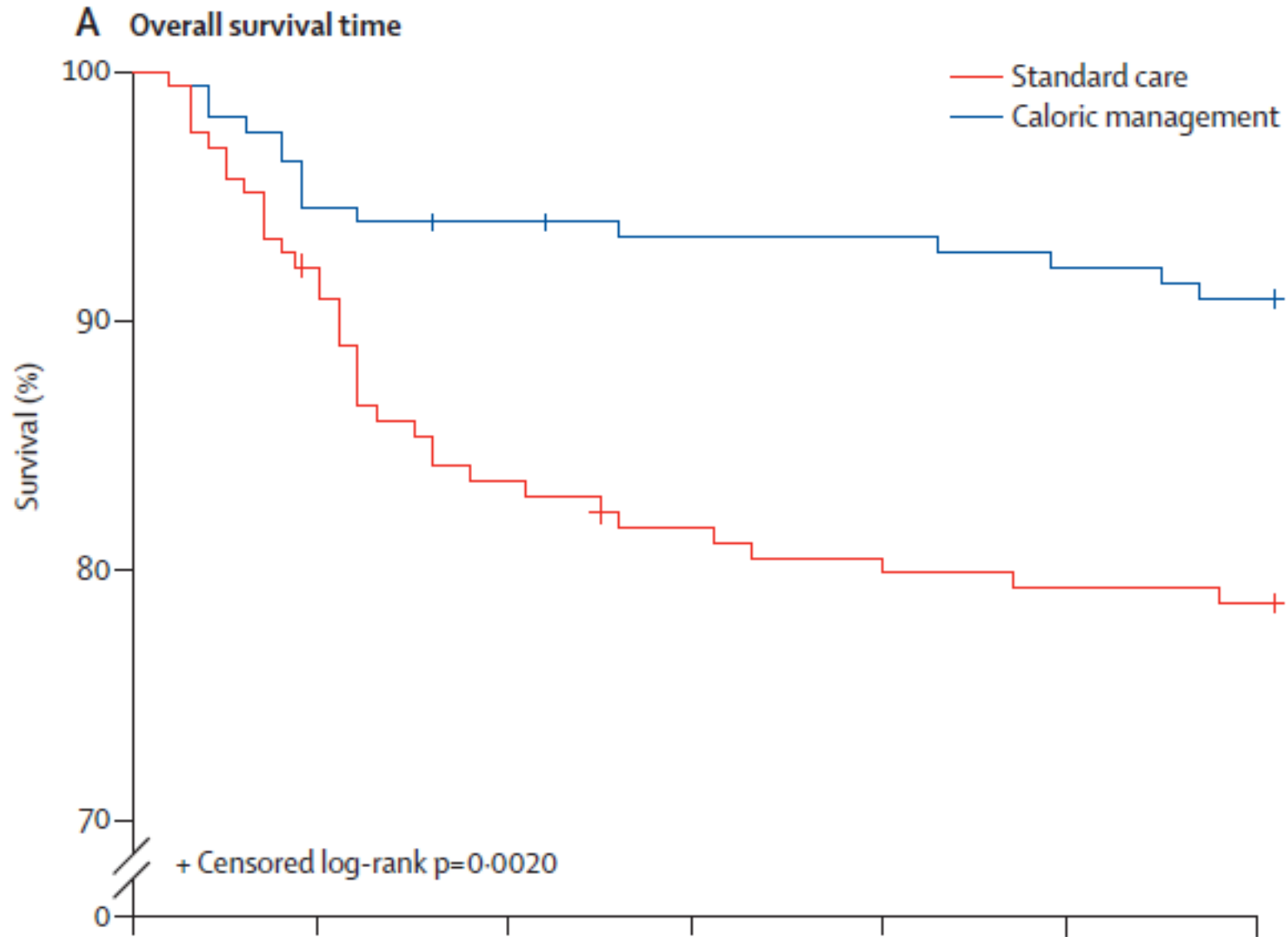
Doig GS, et al. *Lancet Resp Med.* 2015;3(12):943-52.

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

	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 (-0.08 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

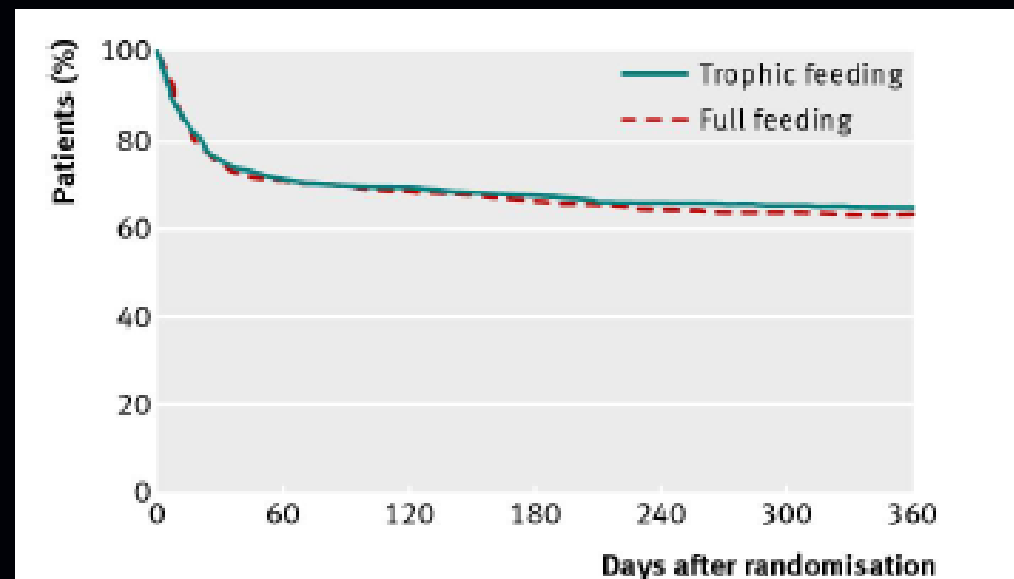
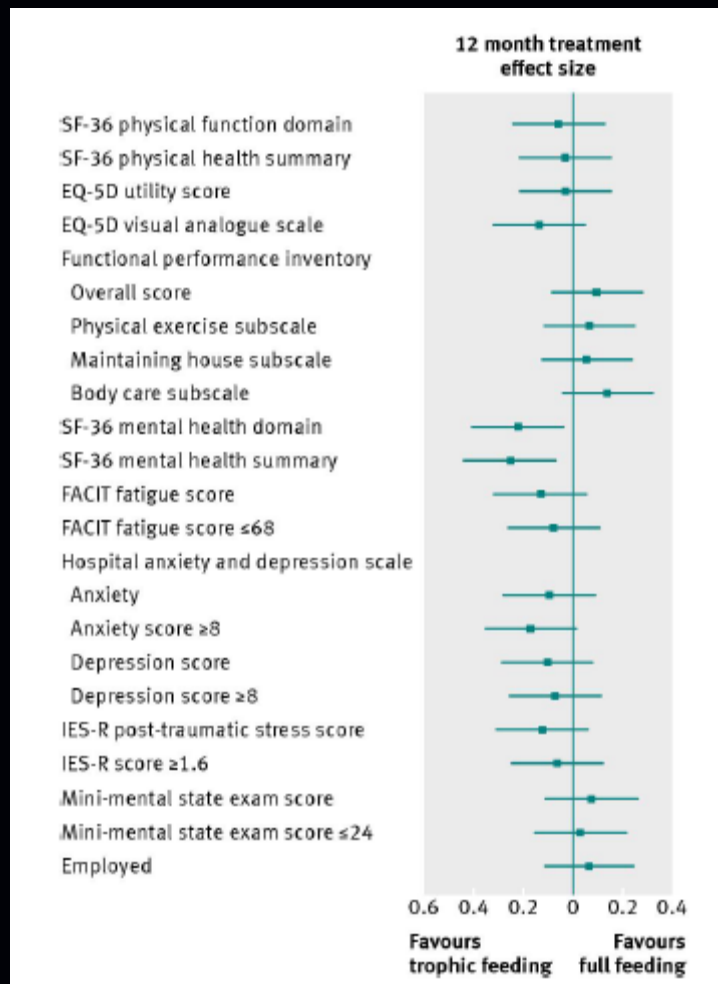
Restricted versus continued standard caloric intake during

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Doig GS, et al. *Lancet Resp Med.* 2015;3(12):943-52.

One year outcomes in patients with acute lung injury randomised to initial trophic or full enteral feeding: prospective follow-up of EDEN randomised trial



Physical and Cognitive Performance of Patients with Acute Lung Injury 1 Year after Initial Trophic versus Full Enteral Feeding

EDEN Trial Follow-up

TABLE 3. TWELVE-MONTH RESULTS BY TREATMENT GROUP*

	Trophic Feeding (n = 75)	Full Feeding (n = 74)	Treatment Effect (95% CI) [†]	P Value [‡]
Physical outcomes				
6-min-walk distance, % predicted	63 (25)	70 (24)	-6 (-14, 2)	0.136
4-m timed walk speed, m/s	0.98 (0.29)	1.08 (0.29)	-0.07 (-0.16, 0.02)	0.125
Manual Muscle Test score	55.9 (4.0)	56.2 (5.2)	-0.1 (-1.6, 1.4)	0.901
Manual Muscle Test score < 48, no. (%)	3 (4)	3 (5)	0.84 (0.16, 4.39)	0.833
Hand grip strength, % predicted	82 (27)	85 (26)	-3 (-12, 5)	0.462
Maximal inspiratory pressure, % predicted	97 (33)	99 (31)	-4 (-15, 6)	0.421
FEV ₁ , % predicted	77 (19)	80 (19)	-2 (-9, 4)	0.424
FVC, % predicted	78 (18)	83 (19)	-4 (-10, 1)	0.144
Body mass index, kg/m ²	29.5 (7.2)	29.6 (9.1)	0.0 (-2.9, 2.8)	0.985
Arm fat area, %	38.9 (12.1)	39.7 (11.5)	-1.2 (-4.9, 2.6)	0.550
Arm muscle area, %	50.8 (10.7)	50.4 (10.0)	0.7 (-2.7, 4)	0.703
Cognitive outcomes				
Cognitive impairment, no. (%)	22 (29)	15 (20)	1.45 (0.71, 3)	0.311
COWA	32 (13)	34 (13)	-2 (-6, 2)	0.431
COWA, ≤1.5 SDs, no. (%)	18 (24)	18 (24)	0.93 (0.44, 1.95)	0.843
Digit Span	9.8 (3.2)	9.9 (3.1)	0.1 (-0.8, 1.1)	0.800
Digit Span, ≤1.5 SDs, no. (%)	6 (8)	4 (5)	1.57 (0.41, 6.06)	0.512
Hayling Sentence Completion	5.5 (1.6)	5.2 (1.8)	0.4 (-0.1, 1.0)	0.119
Hayling, ≤1.5 SDs, no. (%)	7 (10)	14 (19)	0.38 (0.14, 1.03)	0.058
Logical Memory I	9.3 (3.4)	9.9 (3.4)	-0.5 (-1.5, 0.6)	0.379
Logical Memory I, ≤1.5 SDs, no. (%)	13 (18)	9 (12)	1.58 (0.65, 3.85)	0.316
Logical Memory II	9.0 (3.0)	9.4 (3.2)	-0.4 (-1.4, 0.6)	0.443
Logical Memory II, ≤1.5 SDs, no. (%)	10 (14)	7 (10)	1.49 (0.56, 3.92)	0.423
Similarities	9.8 (3.3)	10.5 (3.4)	-0.2 (-1.3, 0.8)	0.648
Similarities, ≤1.5 SDs, no. (%)	8 (11)	7 (10)	1.02 (0.36, 2.83)	0.976

Needham DM, et al. *AJRCCM*. 2013;188(5):567-576.

Dosing of EN

NEW



- **No EN if low nutritional risk, low dz severity
(NRS 2002 \leq 3 or Nutric Score \leq 5) for first week^{1,2}**
- **Trophic or full feeds appropriate for ALI/ARDS and pts
expected to be on MV \geq 72 hrs³**
- **Advance to goal as tolerated over 24-48 hrs
If high nutrition risk (NRS 2002 \geq 5, Nutric \geq 6)^{1,2}
Attempt to provide $>$ 80% goal⁴**

¹Kondrup J (Clin Nutr 2002) ²Heyland DK (Clin Nutr 2015)

³Rice T (JAMA 2012) ⁴Heyland DK (CCM 2011;39:1)

**Should Indirect Calorimetry Be
Used to Determine How Much
to Feed Critically Ill Patients?**

Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial

Claudia Paula Heidegger, Mette M Berger, Séverine Graf, Walter Zingg, Patrice Darmon, Michael C Costanza, Ronan Thibault, Claude Pichard

- **2 hospitals in Switzerland**
- **305 pts receiving <60% of target EN on day 3**
 - Expected ICU > 5 days; survival > 7 days
 - Excl: on TPN, pregnant, GI dysfxn or ileus
- **Randomized to EN (n=152) vs suppl PN d 4-8**
- **Primary Endpoint: Infection b/w d 9-28**
- **61 yo; APACHE 23; 45% surg; 45% infxn on adm**

Heidegger CP, et al. *Lancet*. 2013;381:385-93.

IC: Supplementing EN with PN

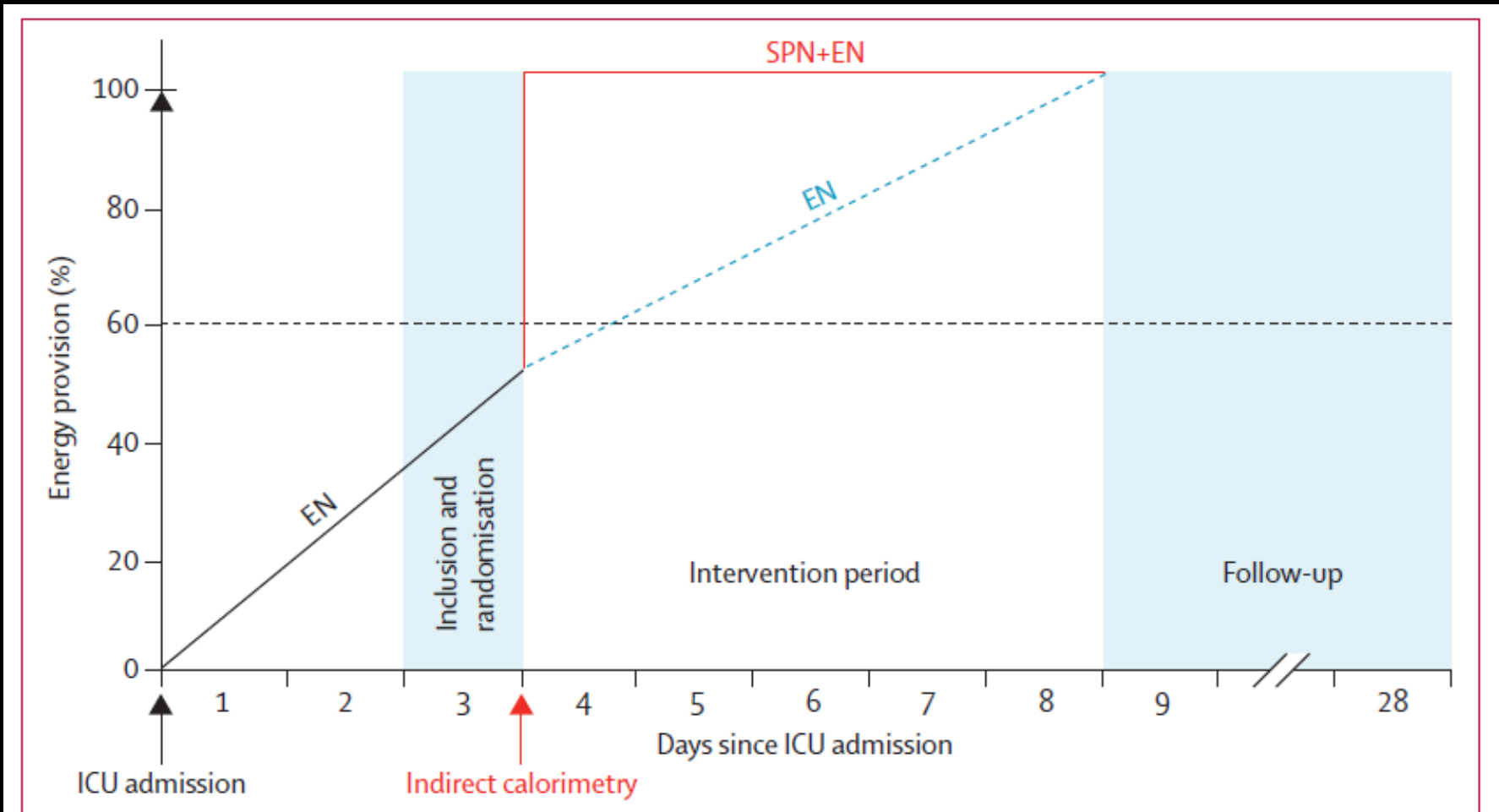
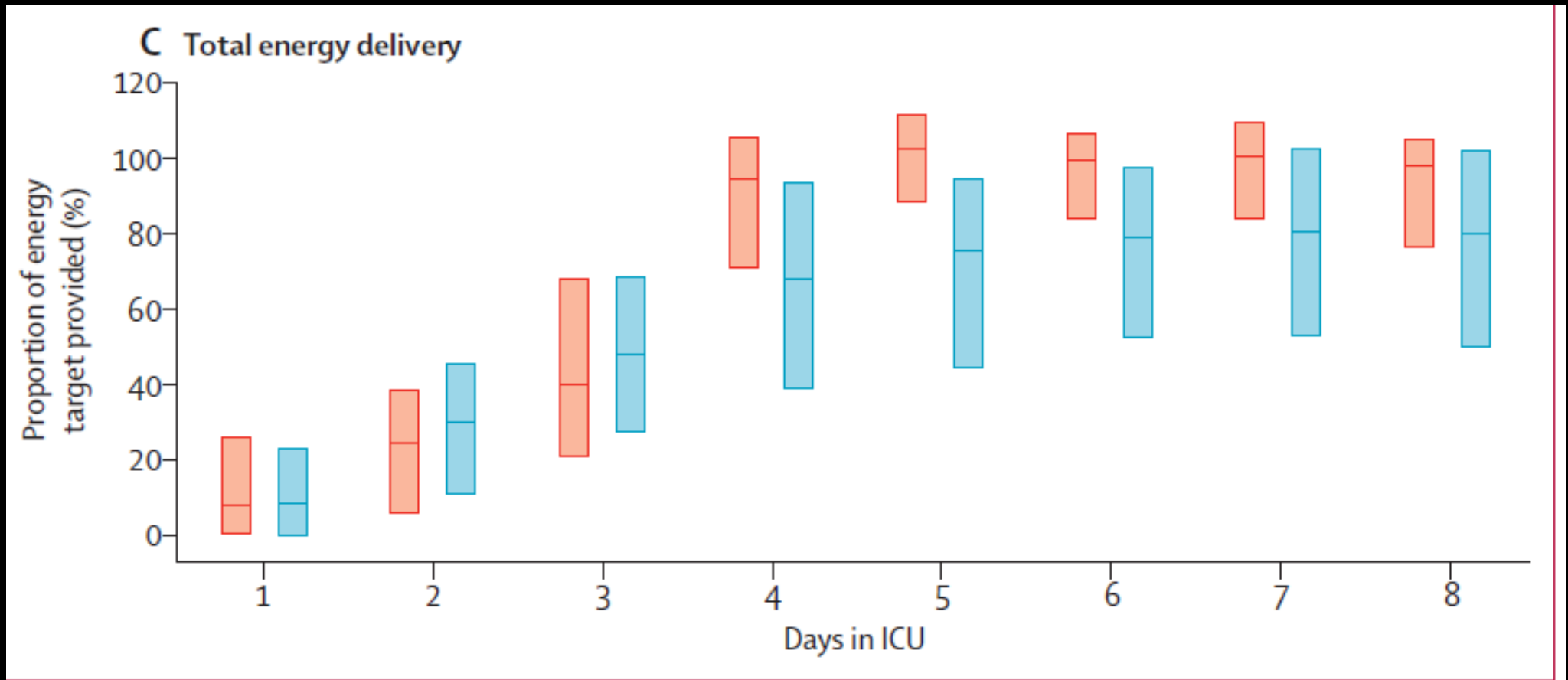


Figure 1: Trial design

Heidegger CP, et al. *Lancet*. 2013;381:385-93.

IC: Supplementing EN with PN



IC: Supplementing EN with PN

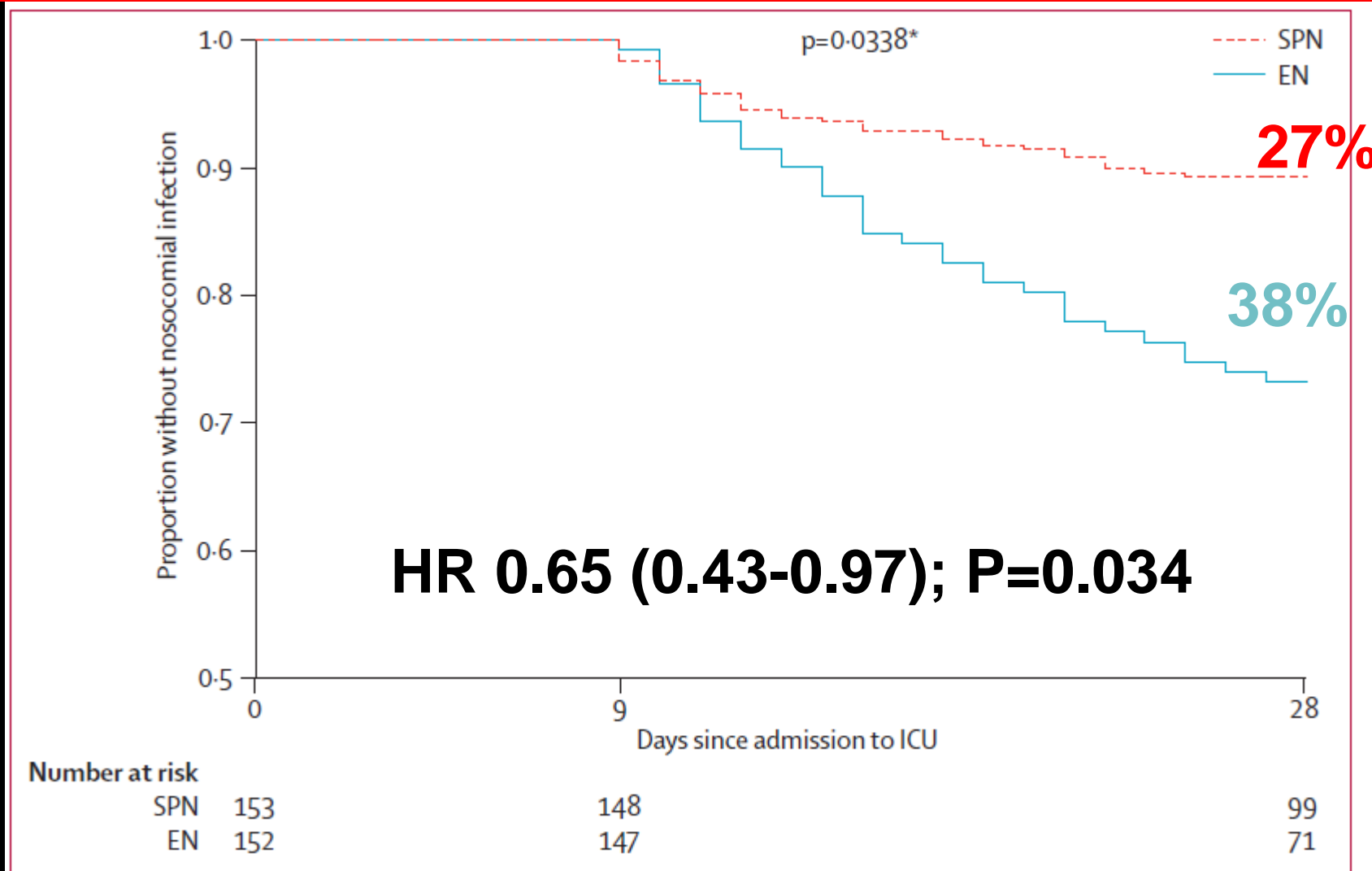


Figure 4: Kaplan-Meier analysis of nosocomial infections

Heidegger CP, et al. *Lancet*. 2013;381:385-93.

IC: Supplementing EN with PN

	Intervention period (days 4-8)		Follow-up (days 9-28)	
	SPN	EN	SPN	EN
Pneumonia	35 (67%)	28 (65%)	22 (46%)	32 (45%)
Bloodstream infection	10 (19%)	6 (14%)	9 (19%)	13 (18%)
Urogenital infection	4 (8%)	2 (5%)	7 (15%)	5 (7%)
Abdominal infection	1 (2%)	4 (9%)	8 (17%)	8 (11%)
Other infection*	2 (4%)	3 (7%)	2 (4%)	13 (18%)

Data are number of events (%). Patients can have one or more infections. Comparisons by type of infections were not significant for the intervention period ($p=0.4866$) or follow-up period ($p=0.1476$). SPN=supplemental parenteral nutrition. EN=enteral nutrition. *Skin, bone, soft tissue, ear, nose, throat, upper respiratory, and non-pulmonary intrathoracic infections.

Table 3: Distribution of nosocomial infections during intervention and follow-up

IC: Supplementing EN with PN

	SPN (n=153)		EN (n=152)		p value	Coefficient (95% CI)
	Mean (SD) or n (%)	95% CI	Mean (SD) or n (%)	95% CI		
Duration of study (days 1-28)						
Antibiotic days for nosocomial infections*	5 (7)	4-6	6 (7)	5-7	0.0298	-0.3 (-0.6 to -0.0)
Antibiotic days	11 (8)	9-12	13 (9)	11-14	0.0257	-2.2 (-4.2 to -0.3)
Antibiotic-free days	15 (9)	14-17	13 (10)	11-14	0.0126	2.7 (0.6 to 4.8)
Hours on mechanical ventilation in all patients‡	153 (163)	126-178	166 (160)	138-189	0.2912	-0.1 (-0.3 to 0.1)
Hours on mechanical ventilation in patients without nosocomial infection‡	83 (101)	58-105	108 (115)	77-135	0.0747	-0.3 (-0.6 to 0.0)
Days in ICU	13 (10)	11-14	13 (11)	12-14	0.2592	-1.3 (-3.5 to 1.0)
Days in hospital	31 (23)	29-38	32 (23)	29-39	0.8781	-0.4 (-5.9 to 5.0)
ICU mortality§	8 (5%)	3-10	12 (7%)	5-13	0.2118	0.6 (0.2 to 1.6)
General mortality§	20 (13%)	9-19	28 (18%)	13-25	0.1193	0.6 (0.3 to 1.2)

Linear regression analyses were done for all secondary outcomes (adjusted for Simplified Acute Physiology II [SAPS II] score, hospital, and admission category) except for antibiotic days for nosocomial infections, hours on mechanical ventilation, and mortality. SPN=supplemental parenteral nutrition. EN=enteral nutrition. ICU=intensive-care unit. *Negative binomial regression analysis was adjusted for SAPS II score, hospital, and admission category. †Statistically significant with Benjamini-Hochberg correction. ‡Negative binomial regression analysis was adjusted for SAPS II score, hospital, and admission category, and controlled for length of ICU stay. §Cox proportional hazard ratios, adjusted for SAPS II score, hospital, and admission category.

Table 4: Secondary outcomes during follow-up and throughout duration of study



Early goal-directed nutrition versus standard of care in adult intensive care patients: the single-centre, randomised, outcome assessor-blinded EAT-ICU trial

- **Open-label, RCT at single center in Denmark**
- **199 mech vent pts expected ICU stay > 3 days**
 - < 24 hrs from ICU admission; Had central line
 - Excl: BMI < 17 or appeared malnourished
- **Randomized to EGDN (n=100) vs usual care**
- **Primary Endpoint: Physical Component Summary of SF 36 at 6 months**



Early goal-directed nutrition versus standard of care in adult intensive care patients: the single-centre, randomised, outcome assessor-blinded EAT-ICU trial

- **EGDN (Early Goal Directed Nutrition) – from d1**
 - Use Indirect Calorimetry to estimate calorie needs
 - Use Urine Urea Nitrogen to estimate protein needs
 - Use EN and Suppl PN to meet cal and protein needs
- **Usual Care**
 - Target 25 kcal / kg / day of calories with EN
 - Add supplemental PN on day 7 if not meeting

Early goal-directed nutrition versus standard of care in adult intensive care patients: the single-centre, randomised, outcome assessor-blinded EAT-ICU trial

Table 2 Nutrition characteristics in ICU after randomisation

Variable	Early goal-directed nutrition (N = 100)	Standard of care (N = 99)
Measured ^a energy requirement, kcal/day	2069 (1816–2380)	1887 (1674–2244)
Calculated ^b energy requirement, kcal/day	1950 (1750–2125)	1875 (1650–2100)
Energy intake, kcal/day	1877 (1567–2254)	1061 (745–1470)
Energy balance ^c , kcal/day	−66 (−157 to −6)	−787 (−1223 to −333)
Measured ^d protein requirement, g/kg/day	1.63 (1.36–2.05)	1.16 (0.89–1.62)
Protein intake, g/kg/day	1.47 (1.13–1.69)	0.50 (0.29–0.69)
Protein balance ^c , g/kg/day	−0.28 (−0.76 to 0.11)	−0.69 (−1.02 to −0.38)
Plasma urea, mmol/l	13.5 (8.7–21.9)	9.0 (5.6–14.4)
24-h urinary urea, mmol/day	516 (368–760)	320 (175–482)

Early goal-directed nutrition versus standard of care in adult intensive care patients: the single-centre, randomised, outcome assessor-blinded EAT-ICU trial

Table 3 Primary and secondary outcome measures in the two intervention groups

Primary outcome measure	Early goal-directed nutrition (N = 100)	Standard of care (N = 99)	Adjusted mean difference (95% CI)	p value
PCS score at 6 months adjusted for presence of haematologic malignancy, mean (SD)	22.9 (21.8)	23.0 (22.3)	-0.0 ^a (-5.9 to 5.8)	0.99
Secondary outcome measures	Early goal-directed nutrition (N = 100)	Standard of care (N = 99)	Relative risk or mean difference (95% CI)	p value
Vital status, no. (%)				
Dead at day 28	20 (20%)	21 (21%)	0.94 (0.55-1.63)	0.83
Dead at day 90	30 (30%)	32 (32%)	0.93 (0.61-1.40)	0.72
Dead at 6 months	37 (37%)	34 (34%)	1.08 (0.74-1.57)	0.70
Length of stay among 6-month survivors, median days (IQR)				
ICU	7 (5-22)	7 (4-11)	NA	0.21
Hospital	30 (12-53)	34 (14-53)	NA	1.00

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Secondary outcome measures	Early goal-directed nutrition (N = 100)	Standard of care (N = 99)	Relative risk or mean difference (95% CI)	p value
Percentage of days alive without life support at day 90, median (IQR)				
RRT	100% (97–100)	100% (97–100)	NA	0.64
Mechanical ventilation	86% (39–96)	92% (56–96)	NA	0.27
Inotrope/vasopressor support	96% (82–98)	96% (84–98)	NA	0.67
Time to new organ failure, mean days (SD)	5.4 (0.4)	5.9 (0.5)	NA	0.33 ^b
New organ failure in ICU, no. (%)	81 (81%)	77 (78%)	1.04 (0.90–1.20)	0.57
Time to death, mean days (SD)	60 (13)	91 (24)	NA	0.51 ^c
New use of RRT in ICU, no. (%)	22 (22%)	17 (17%)	1.28 (0.73–2.26)	0.39
Time to any infection, mean days (SD)	20 (1)	51 (9)	NA	0.80 ^b
Nosocomial infections, no. (%)				
Any	19 (19%)	12 (12%)	1.57 (0.80–3.05)	0.18 ^d
Pneumonia	4 (4%)	4 (4%)		
Bloodstream infection	5 (5%)	4 (4%)		
CVC-related sepsis	3 (3%)	0 (0%)		
Intra-abdominal infection	3 (3%)	3 (3%)		
Urogenital sepsis	5 (5%)	1 (1%)		
Skin and soft-tissue infection	3 (3%)	0 (0%)		
Severe adverse reaction, no. (%)	1 (1%)	2 (2%)	NA	– ^e
Mental component summary score at 6 months, mean (SD)	23.6 (24.5)	26.8 (25.0)	–3.1 (–10.5 to 4.2)	0.40

Case

- **55 y.o. male COPD with baseline PaCO₂ 55, NIDDM, HTN, atrial fibrillation (on coumadin) presents with pneumonia and septic shock. He has new renal failure with creatinine 5.0. Intubated in ED, started on norepinephrine drip, and admitted to MICU. On 70% FiO₂, PEEP 12 with a CXR that looks like ARDS.**

Nutrition Questions

- **How should we feed him?**
 - Enteral; Gastric
- **When should we start feeding him?**
 - Right away (assuming some hemodynamic stability)
- **What should we feed him?**
 - TF “du jour”, +/- protein supplementation
- **How much should we feed him (goals)?**
 - Trophic vs permissive underfeeding vs. full-calorie; No IC
- **What safety measures should we employ?**
 - No GRV; Clinical Exam

Summary

- **Nutritional Assessments in respiratory failure are not very accurate**
- **TPN for first 5 days appears safe, but did not improve outcomes**
- **Supplementing EN with TPN early in course has limited, if any, benefit (and ? harm)**
- **Limited data suggest starting EN in first 24 hours improves outcomes**
- **Initial Trophic or permissive underfeeding EN had similar outcomes to targeting full EN**

QUESTIONS???