Update Nutrition in Critically Ill Patients

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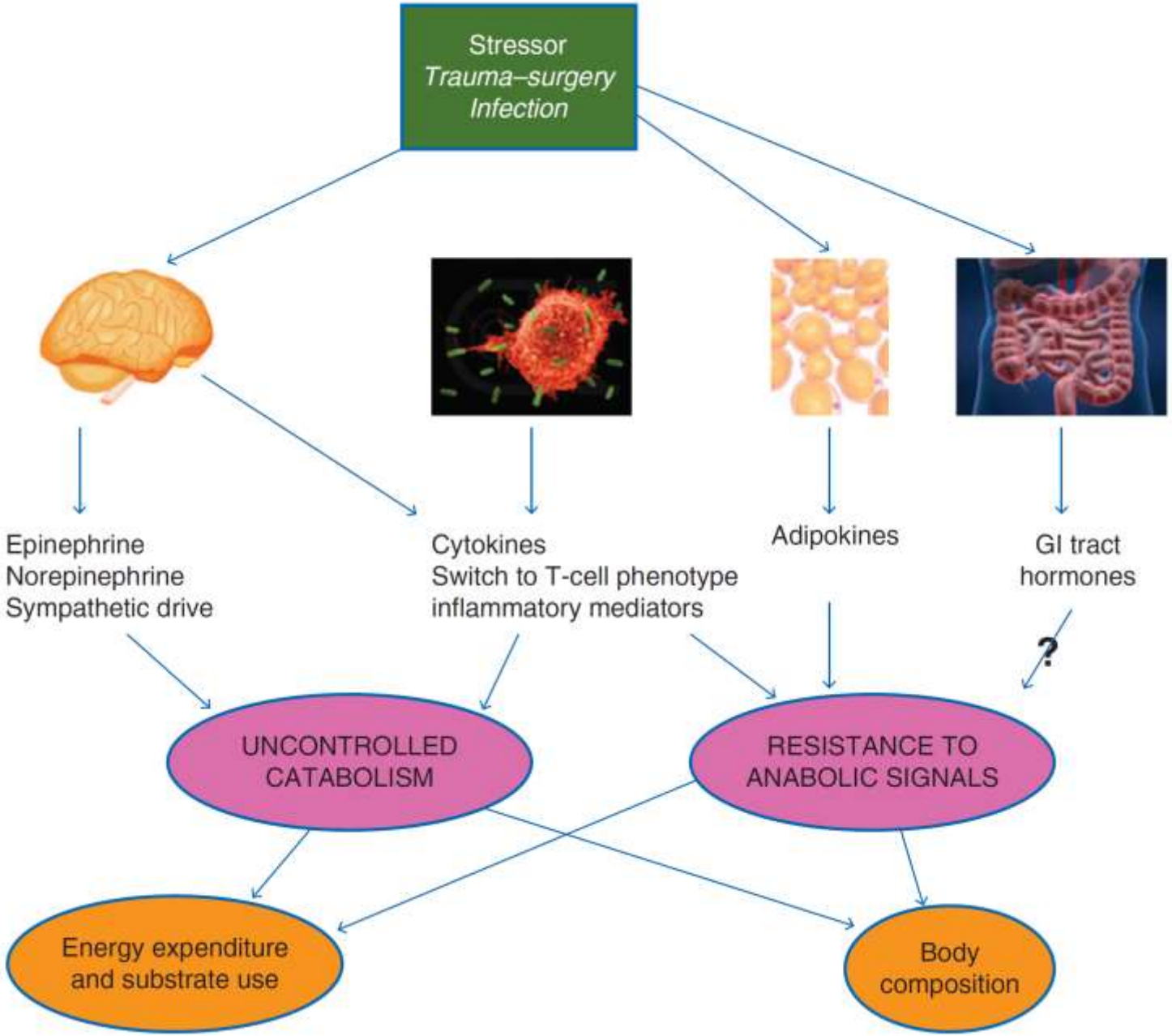
Outlines

- Metabolic response to the stress of critical illness.
- Route
  - PN vs. EN
  - Gastric vs. small bowel feeding
- How much
  - Underfeeding vs Overfeeding
- Protein
  - Should we increase protein delivery during critical illness
- Lipid
  - Does the type of parenteral lipids matter?

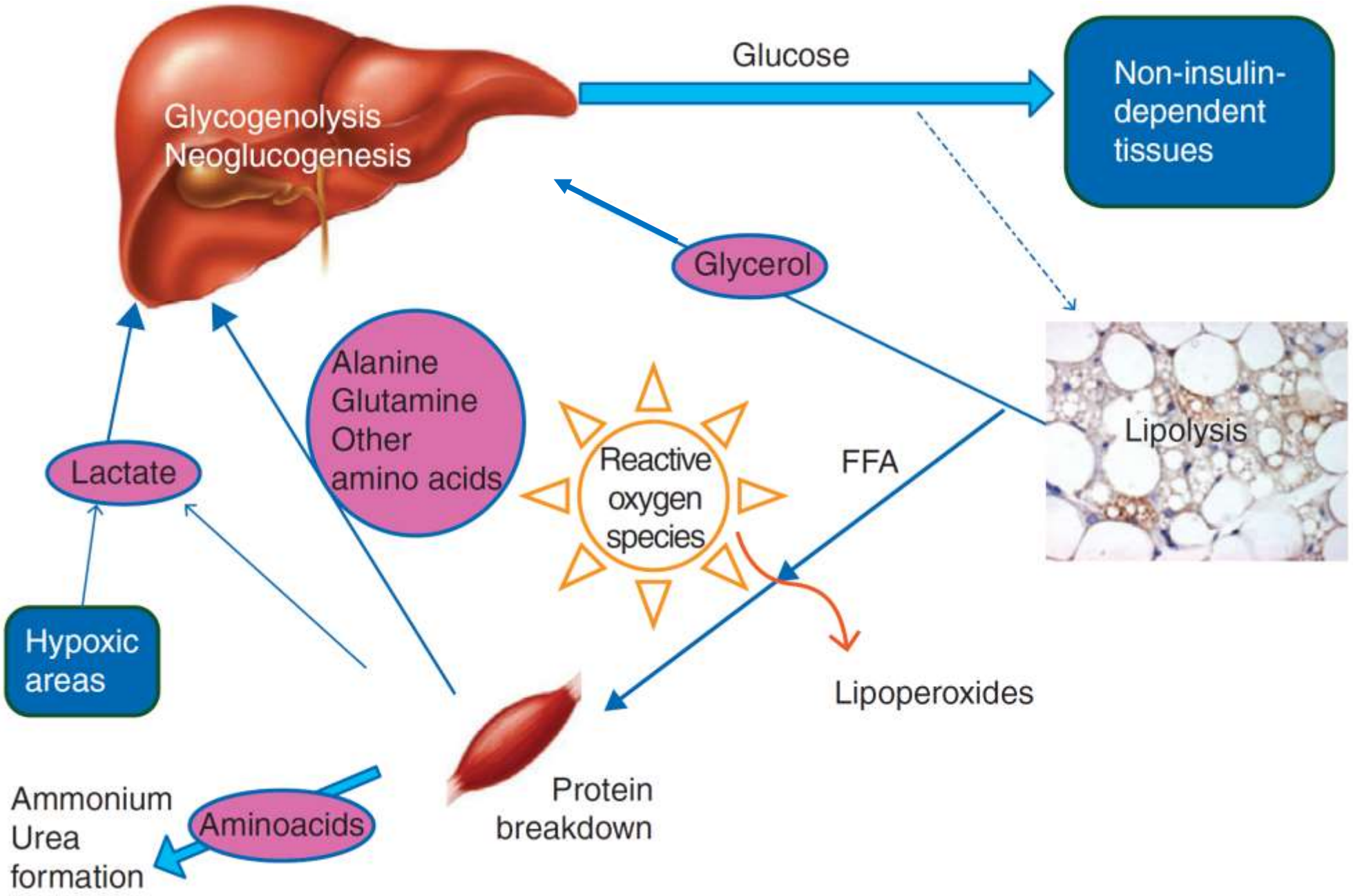


Preiser JC, et al. Br J Anaesth. 2014;113(6):945-54.

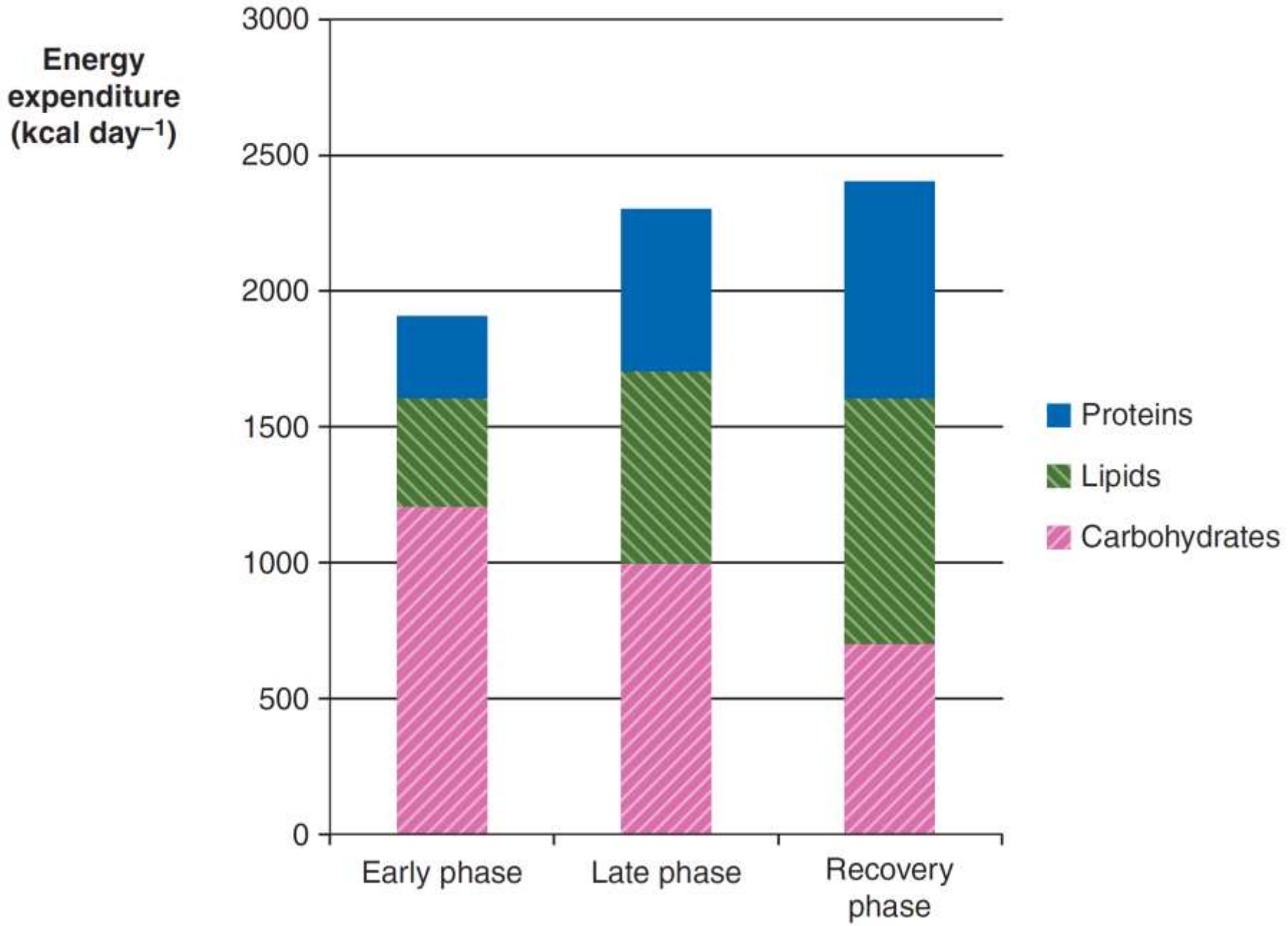
Mechanisms of hormones and cytokines in mediating Stress-induced hyperglycemia

Hormones	Mechanism
Glucagon	Increased gluconeogenesis Increased hepatic glycogenolysis
Epinephrine	Skeletal muscle insulin resistance by altering post receptor signaling Increased gluconeogenesis Increased skeletal muscle and hepatic glycogenolysis Increased lipolysis, increased free fatty acids Direct suppression of insulin secretion
Norepinephrine	Increased lipolysis Increased gluconeogenesis but hyperglycemia not marked except at high conc.
Growth hormone	Skeletal muscle insulin resistance Increased lipolysis
Tumor necrosis factor	Skeletal muscle insulin resistance, altered post receptor signaling Hepatic insulin resistance

McCowen KC, Bistrian BR. *Nutr Clin Pract.* 2004;19(3):235-244.

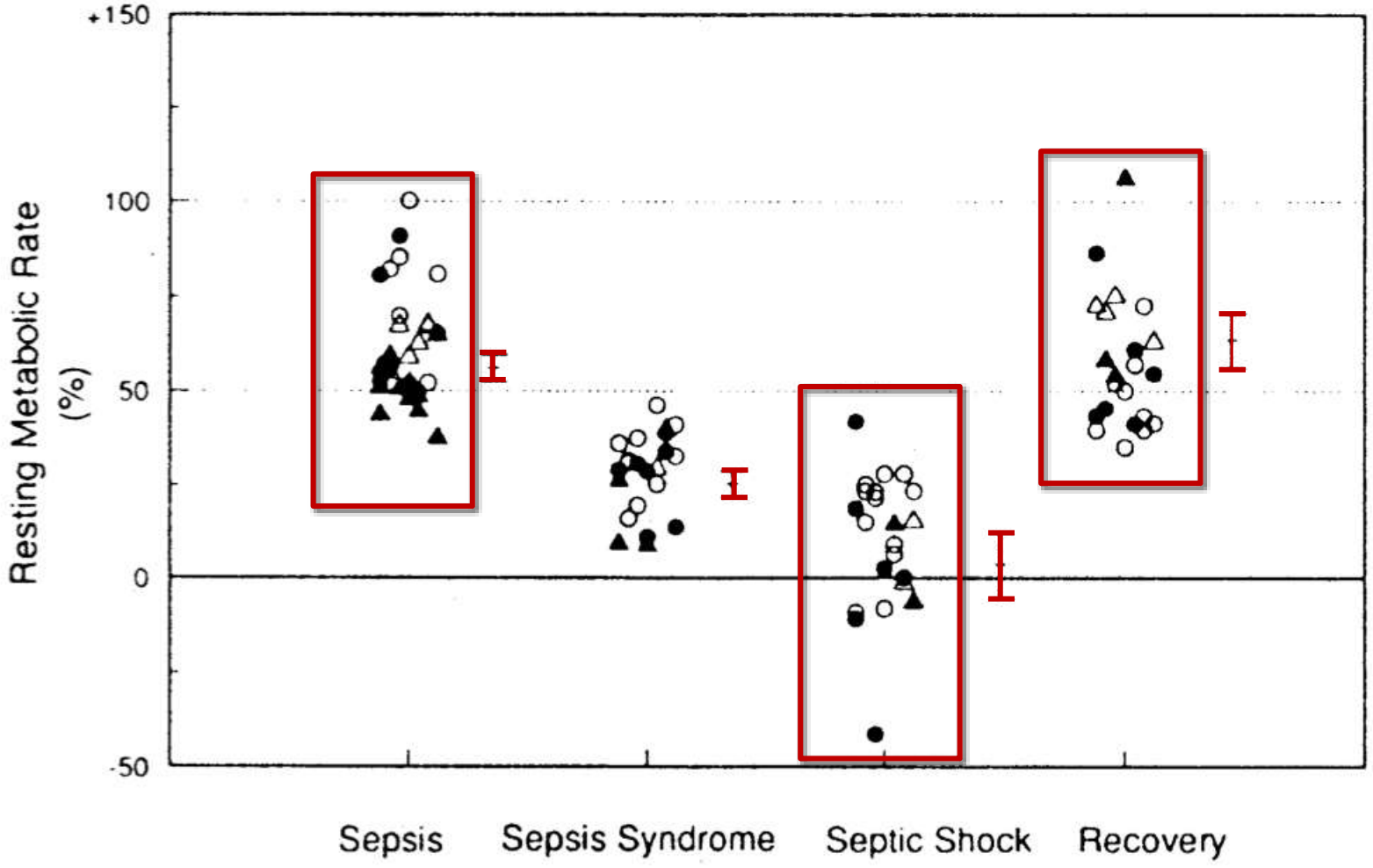


Preiser JC, et al. Br J Anaesth. 2014;113(6):945-54.



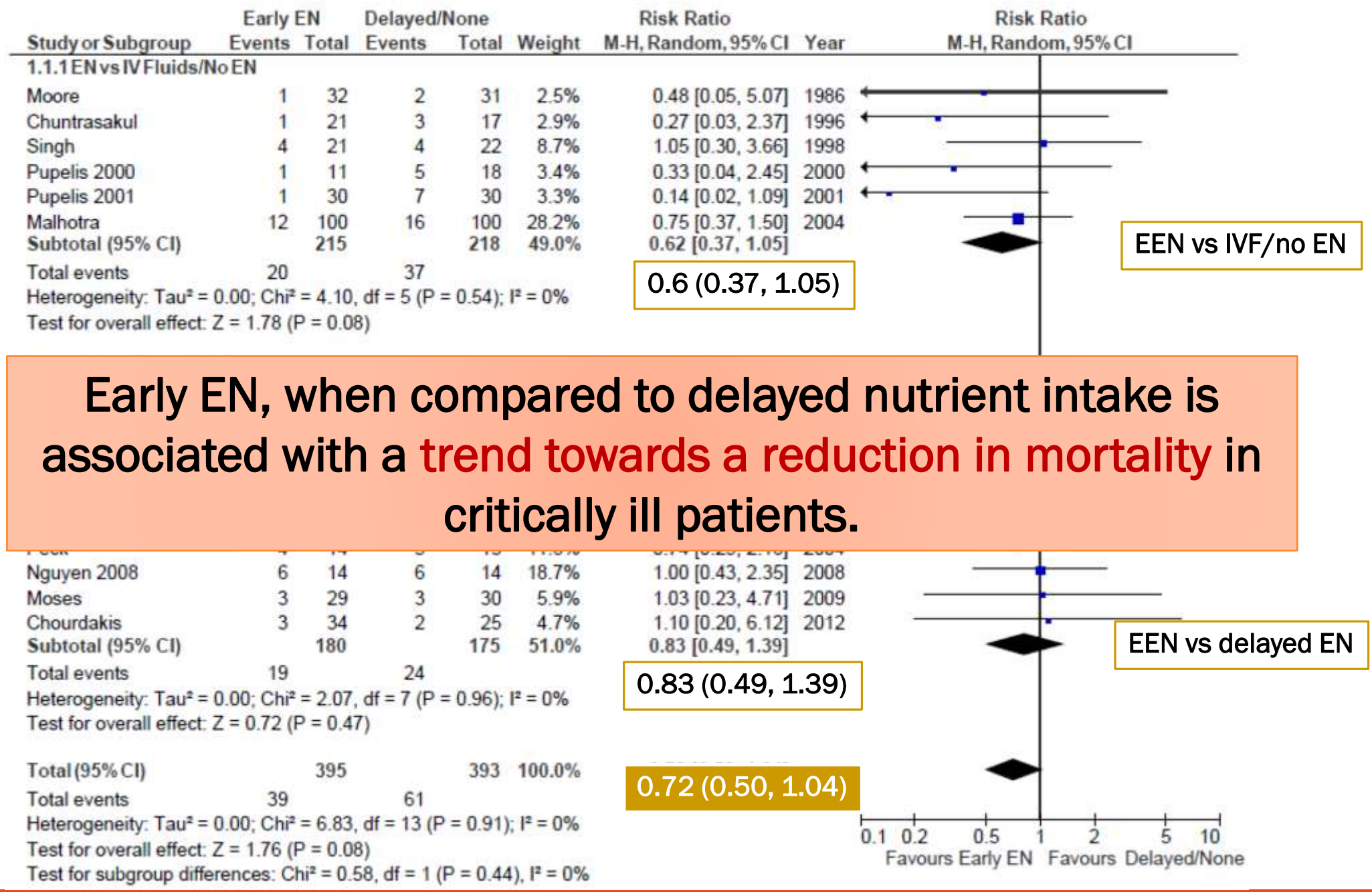
Preiser JC, et al. Br J Anaesth. 2014;113(6):945-54.

Metabolic rate in sepsis

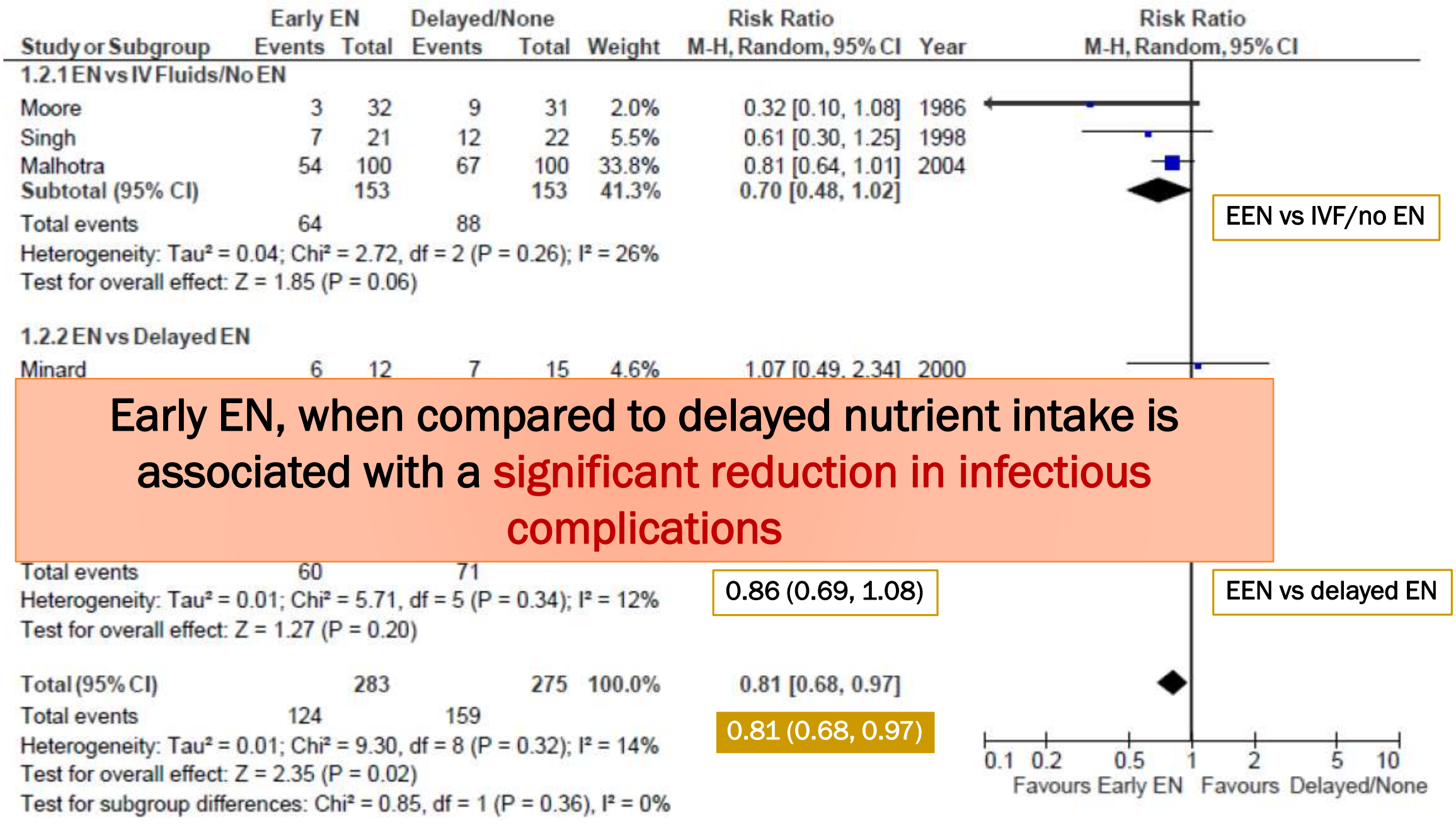


Kreymann et al. Crit Care Med 1993; 21: 1012-19

Early enteral feeding	subject	Timing	Outcomes
Marik, CCM 2001	15 RCTs (n=753) Post-op, trauma, head injury, burn, MICU	<24 h (1 study <36 h)	55% reduction in infection (95%CI:0.3-0.66) Dec. LOS 2.2 d (95%CI:-0.81 to -3.63 d) Significant heterogeneity between studies
Lewis SJ, BMJ 2001	11RCTs (n=837) Post GI surgery	NPO vs <24 h	28% reduction in infection (95%CI:0.54-0.98) Dec. LOS 0.84 d (95%CI:-0.36 to -1.33) Increase Vomiting risk 1.27 (95%CI: 1.01-1.61) Trend to decrease wound dehiscence
Heyland, JPEN 2003	8 RCTs (n=317)	<24-48 h	Trend to reduce infections and mortality
Lewis SJ, J Gastrointest Surg 2009	13 RCTs (n=1173) Post GI Surgery	NPO vs <24 h	59% reduction in mortality (95%CI:0.18-0.93) Dec. LOS 0.89 d (95%CI:-0.2 to -1.5)
Doig GS, Int Care Med 2009	6 RCTs (n=234) adult ICU	<24 h	69% reduction in pneumonia (95%CI:0.12-0.78) 64% reduction in mortality (95%CI:0.14-0.85)
Osland E, JPEN 2011	15 RCTs (n=1240) Post GI Surgery	<24 h	45% reduction in post-op complications (95%CI: 0.35-0.87)
Doig GS, Injury 2011	3 RCTs (n=126) ICU Trauma	<24 h	80% reduction in mortality (95%CI:0.04-0.91)
Li JY, PLoS One 2011	11 RCTs (n=775) Acute pancreatitis	< 48 h	62% reduction in infection (95%CI:0.21-0.68) Dec. LOS 2.18 d (95%CI:-0.87 to -3.48) 69% reduction in mortality (95%CI:0.14-0.71)
Mikhailov TA, JPEN 2014	Retrospective PICU (n=5,105)	<48 h	49% reduction in mortality (95%CI:0.34-0.76) No diff in LOS and MV duration



Early EN, when compared to delayed nutrient intake is associated with a trend towards a reduction in mortality in critically ill patients.



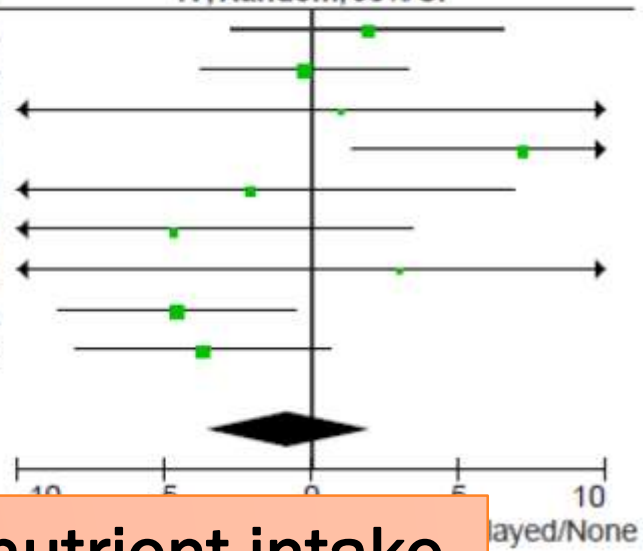
Infectious complications

Figure 3. Studies comparing early EN vs delayed nutrient intake: ICU LOS

Study or Subgroup	Early EN Mean	SD	Total	Delayed/None Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Eyer	11.8	7.9	19	9.9	6.7	19	15.8%	1.90 [-2.76, 6.56]	1993
Chuntrasakul	8.1	6.3	21	8.35	4.8	17	19.5%	-0.25 [-3.78, 3.28]	1996
Pupelis 2000	7	41	11	6	34	18	0.9%	1.00 [-27.87, 29.87]	2000
Minard	18.5	8.8	12	11.3	6.1	15	12.6%	7.20 [1.34, 13.06]	2000
Pupelis 2001	13.9	14.6	30	16	20.5	30	7.1%	-2.10 [-11.11, 6.91]	2001
Kompan 2004	15.9	9.7	27	20.6	18.5	25	8.3%	-4.70 [-12.82, 3.42]	2004
Peck	40	32	14	37	33	13	1.2%	3.00 [-21.55, 27.55]	2004
Nguyen 2008	11.3	3	14	15.9	7.1	14	17.8%	-4.60 [-8.64, -0.56]	2008
Chourdakis	24.8	7.6	34	28.5	8.9	25	16.8%	-3.70 [-8.02, 0.62]	2012
Total (95% CI)			**182**			**176**	**100.0%**	**-0.78 [-3.56, 2.00]**	

Heterogeneity: Tau² = 7.11; Chi² = 14.71, df = 8 (P = 0.06); I² = 46%

Test for ove



Early EN, when compared to delayed nutrient intake has no effect on ICU or hospital length of stay.

Figure 4. Stu

Study or Su								ce % CI	
Chiarelli	69.2	10.4	10	89	18.9	10	17.5%	-19.80 [-33.17, -6.43]	1990
Singh	14	6.9	19	13	7	18	31.2%	1.00 [-3.48, 5.48]	1998
Minard	30	14.7	12	21.3	13.7	15	21.1%	8.70 [-2.13, 19.53]	2000
Pupelis 2000	45	96	11	29	103	18	1.1%	16.00 [-58.04, 90.04]	2000
Pupelis 2001	35.3	22.9	30	35.8	32.5	30	16.5%	-0.50 [-14.73, 13.73]	2001
Peck	60	44	14	60	38	13	5.6%	0.00 [-30.95, 30.95]	2004
Dvorak	53	34.4	7	37.9	14.6	10	7.0%	15.10 [-11.94, 42.14]	2004
Total (95% CI)			**103**			**114**	**100.0%**	**-0.18 [-8.15, 7.80]**	

Heterogeneity: Tau² = 47.83; Chi² = 12.41, df = 6 (P = 0.05); I² = 52%

Test for overall effect: Z = 0.04 (P = 0.97)

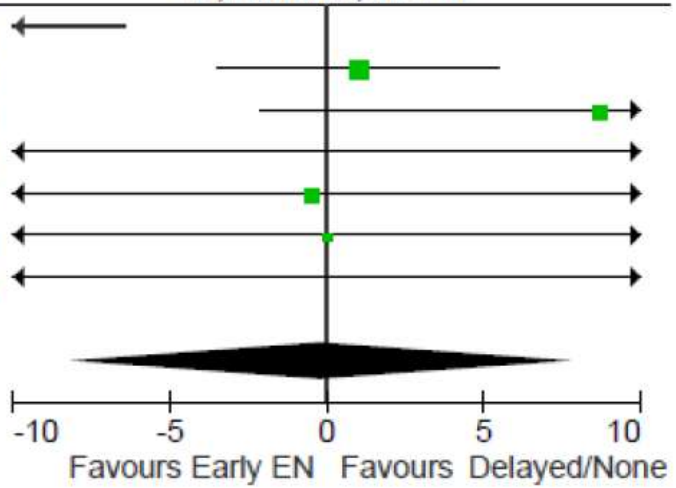
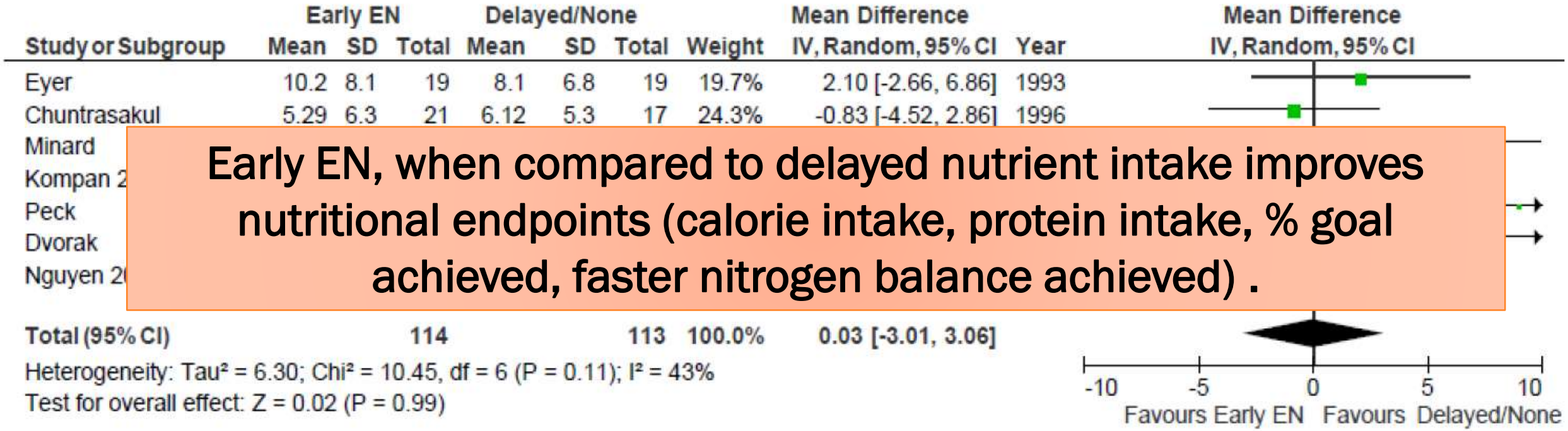


Figure 5. Studies comparing early EN vs delayed nutrient intake: Ventilator days



Early EN, when compared to delayed nutrient intake improves nutritional endpoints (calorie intake, protein intake, % goal achieved, faster nitrogen balance achieved) .

Canadian Clinical Practice Guidelines 2015

Recommend early enteral nutrition (within 24-48 hours following admission to ICU) in critically ill patients

When EN is not enough: Think about combination EN and PN

- Canadian CPG 2013 and 2015
  - Strongly recommend the use of EN over PN (2013) → recommend the use of EN over PN in patients with an intact GI tract
  - Recommend that PN not be started at the same time as EN
  - Recommend that PN not be used routinely, but early PN should be considered in nutritionally high-risk patients with a relative contraindication to early EN
  - Strongly recommend that early SPN and high IV glucose not be used in unselected critically ill patients (i.e. low risk patients with short stay in ICU). In the patient who is not tolerating adequate EN, there are insufficient data to put forward a recommendation about when PN should be initiated.
  - In critically ill patients who are not malnourished, are tolerating some EN, or when PN is indicated for short term use (< 10 days), low dose PN should be considered.

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Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)

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	Recommendation	Quality of evidence	Recommendation strength
Initiate Enteral Nutrition	**Question: What is the benefit of early EN in critically ill adult patients when compared to withholding or delaying this therapy?**		
	B1. We recommend that nutrition support therapy in the form of EN should be initiated within the first 24-48 hours following onset of critical illness.	Very Low	Strong
	Question: Is there a difference in outcomes between the use of EN or PN for adult critically ill patients?		
	B2. We suggest the use of EN over PN in critically ill patients who require nutrition support therapy.	Very Low to Low	Weak.
	Question: Is the clinical evidence of contractility (bowel sounds, flatus) required prior to initiating EN in critically ill adult patients?		
	B3. Based on expert consensus, we suggest that in the majority of medical and surgical ICU patient populations, while gastrointestinal contractility factors should be evaluated when initiating EN, overt signs of contractility should not be required prior to initiation of EN.	Ungraded	
	Question: What is the preferred level of infusion of EN within the GI tract for critically ill patients? How does the level of infusion of EN affect patient outcomes?		
	B4a. We recommend that the level of infusion be diverted lower in the GI tract in those critically ill patients at high risk for aspiration (see section D4) or those who have shown intolerance to gastric EN.	Moderate to High	Strong
	B4b. Based on expert consensus we suggest that in most critically ill patients it is acceptable to initiate EN in the stomach.	Ungraded	

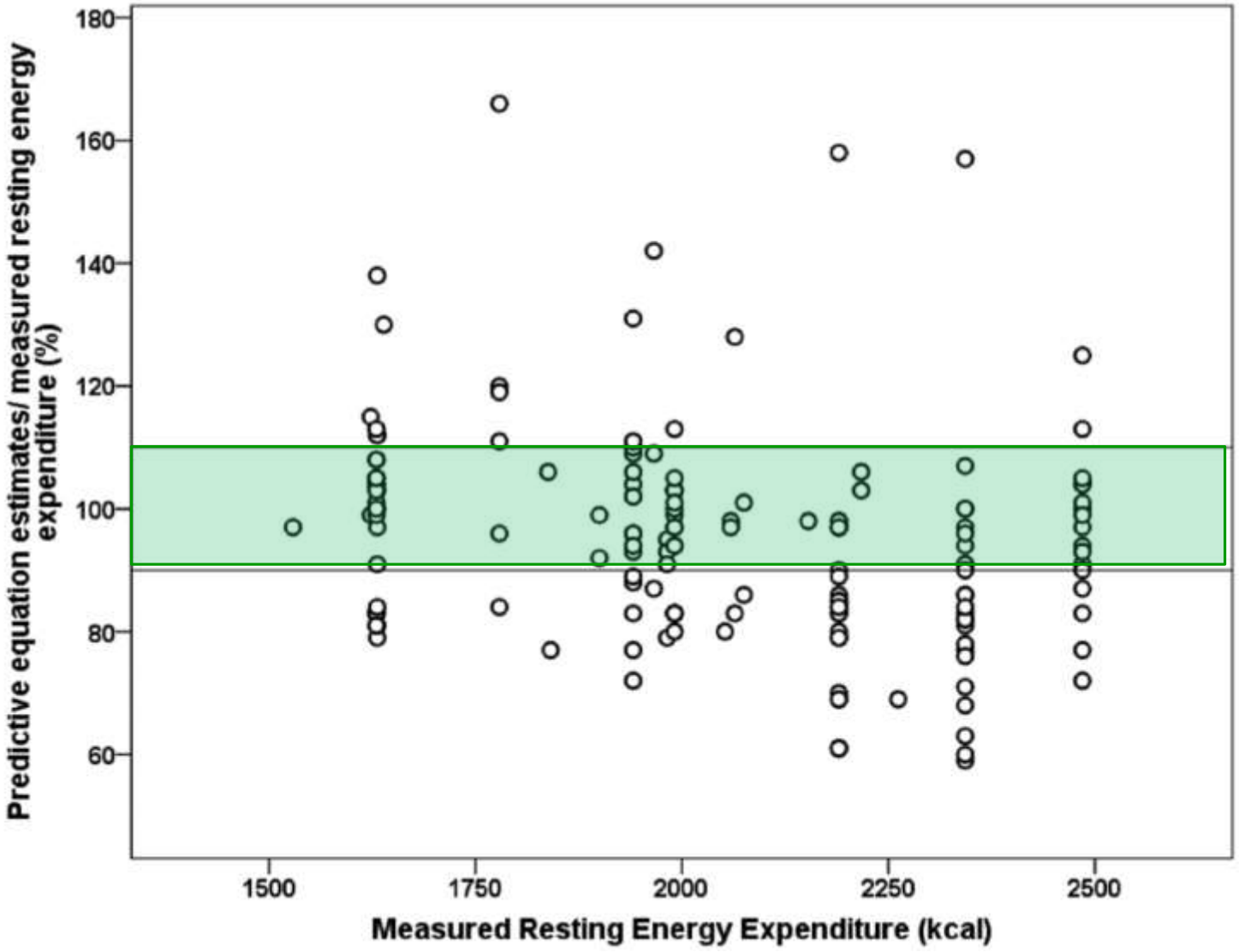
McClave SA, et al. JPEN 2016;40:159-211

Intragastric vs. small intestinal delivery of EN in the critically ill:
a systematic review and meta-analysis

- Data from 15 studies were included.
- Small bowel feeding was associated with
  - a reduced risk of pneumonia (RR, small intestinal vs. intragastric: 0.75 (95% confidence interval 0.60 to 0.93); P = 0.01; I2 = 11%). The point estimate was similar when only studies using microbiological data were included.
  - Duration of ventilation (weighted mean difference: -0.36 days (-2.02 to 1.30); P = 0.65; I2 = 42%), length of ICU stay (WMD: 0.49 days, (-1.36 to 2.33); P = 0.60; I2 = 81%) and mortality (RR 1.01 (0.83 to 1.24); P = 0.92; I2 = 0%) were unaffected by the route of feeding.
  - While data were limited, and there was substantial statistical heterogeneity, there was significantly improved nutrient intake via the small intestinal route (% goal rate received: 11% (5 to 16%); P = 0.0004; I2 = 88%).

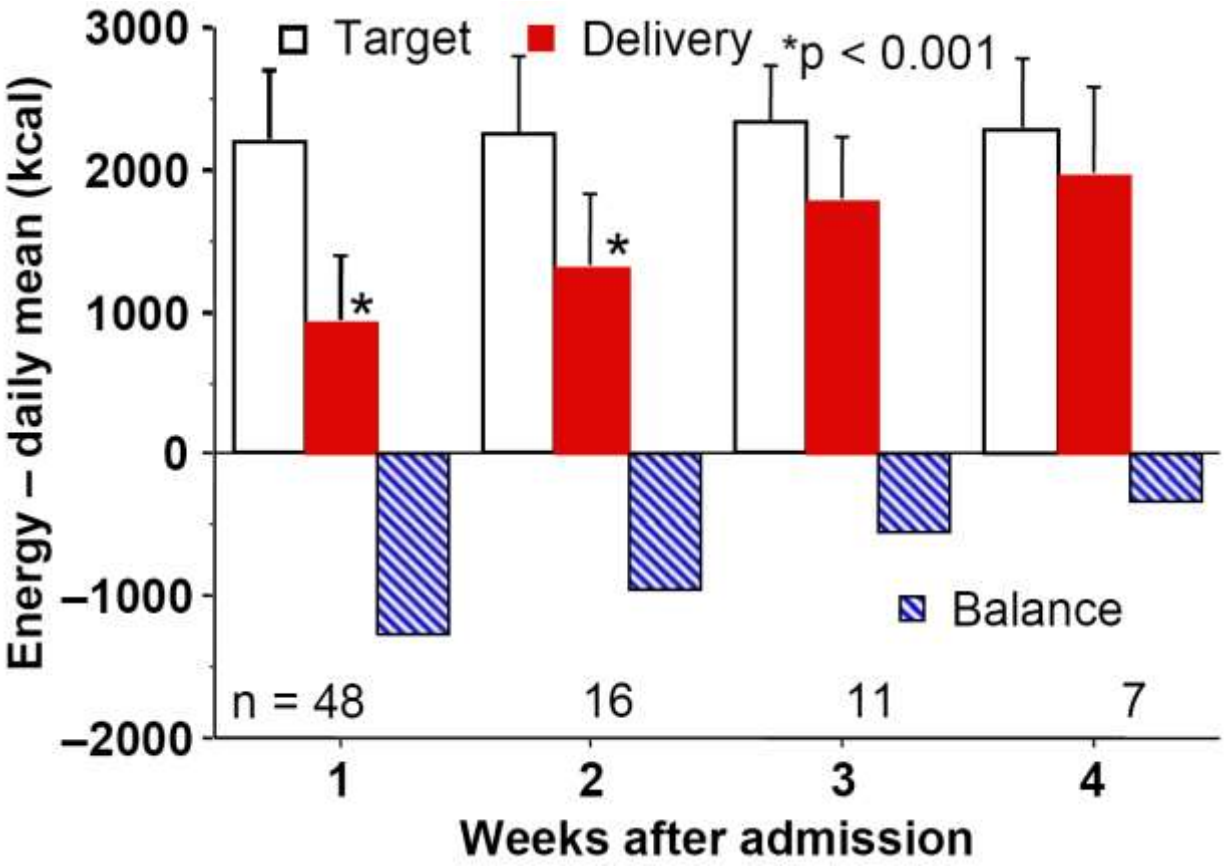
Deane AM, et al. *Crit Care.* 2013;17(3):R125.

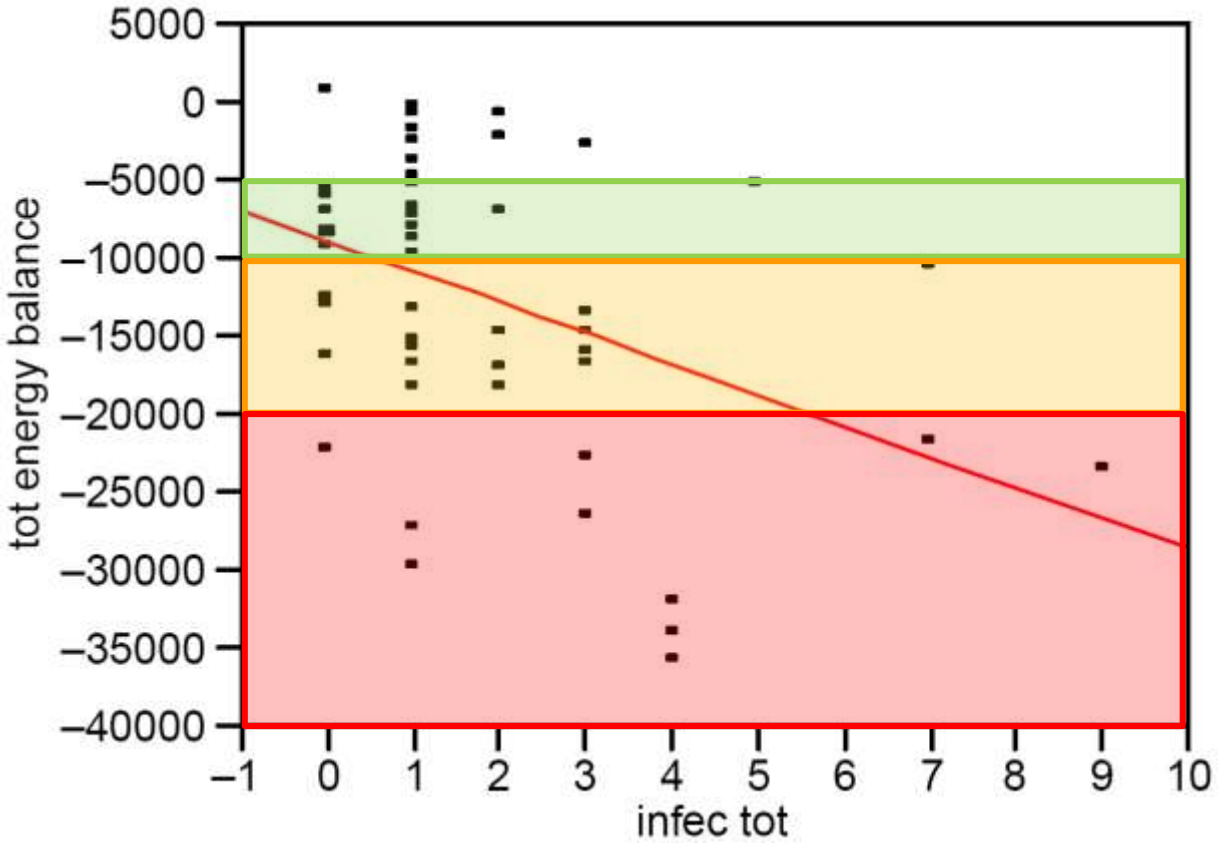
Prevalence of Underprescription or Overprescription of Energy Needs in Critically Ill Mechanically Ventilated Adults as Determined by Indirect Calorimetry



Tatucu-Babet OA, et al. *JPEN* 2016;40(2):212-225.

Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU





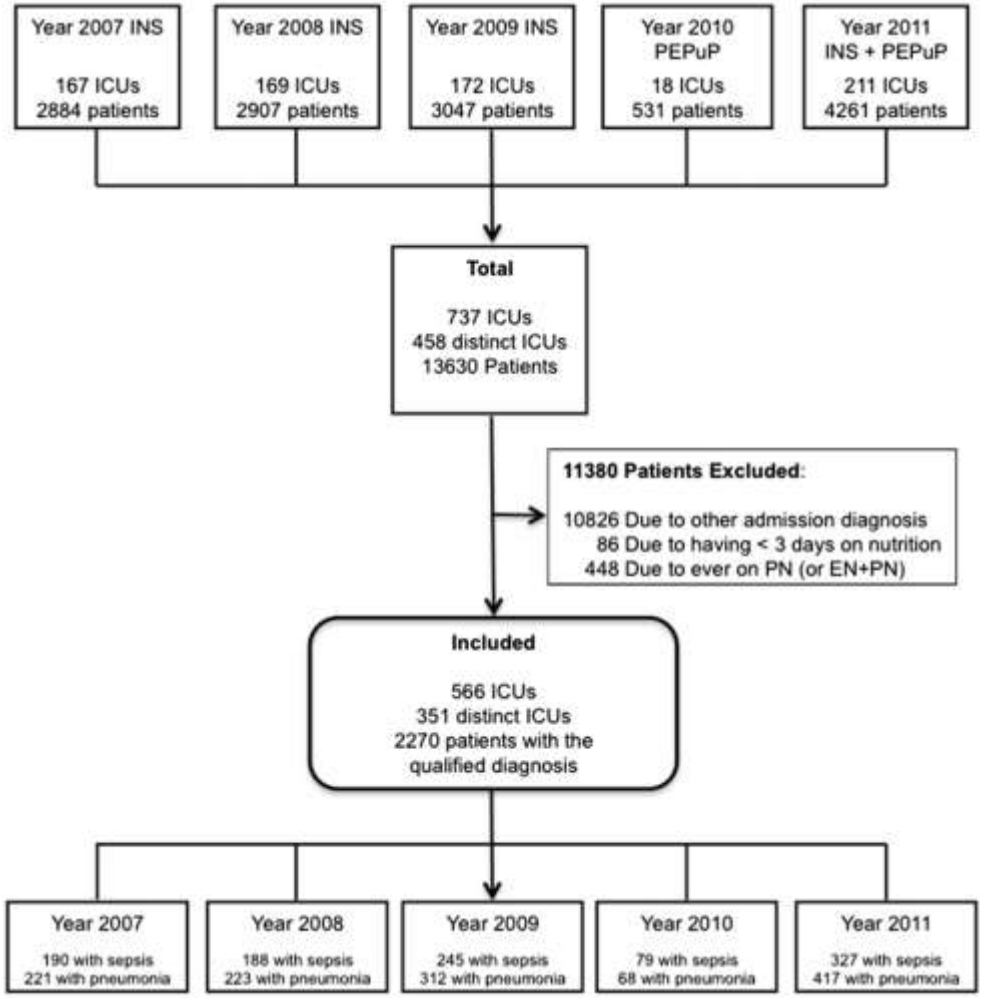
Villet S. Clin Nutr 2005;24:502-9

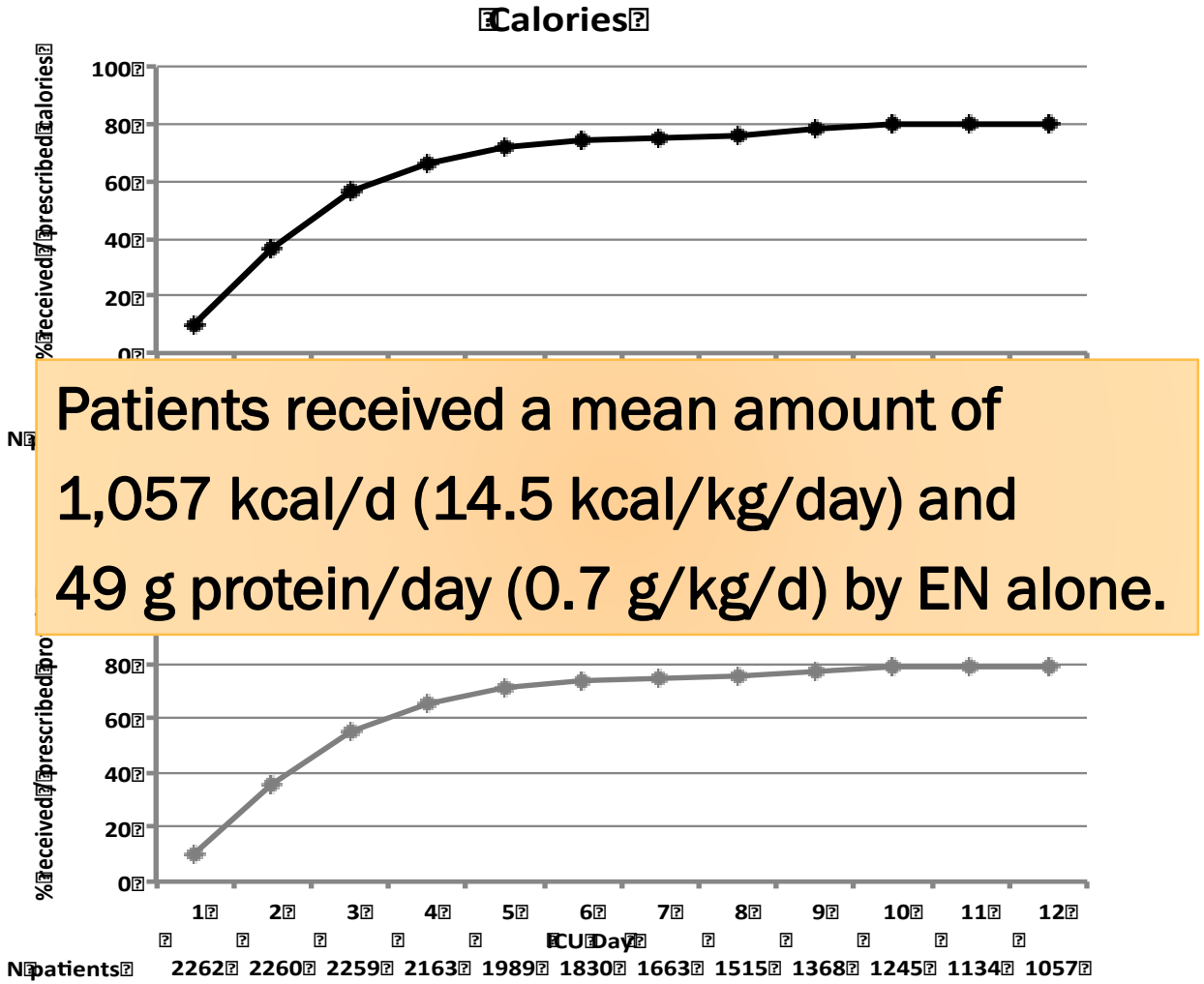
Inadequate energy delivery during early critical illness correlates with increased risk of mortality

Clinical outcomes	1st to 7th day		
	Low ED	High ED	P
Length of Hospital stay	32.4 ± 22.7	38.6 ± 30.9	0.203
Length of ICU stay	14.4 ± 5.2	14.7 ± 5.5	0.746
Ventilator free time	3.0 ± 3.2	3.8 ± 4.0	0.291
ICU mortality	19 (42.2%)	41 (16.4%)	<0.001*

Clinical outcomes	1st to 7th day		
	Low PD	High PD	P
Length of Hospital stay	36.3 ± 31.5	37.9 ± 29.6	0.733
Length of ICU stay	14.7 ± 5.0	14.6 ± 5.5	0.942
Ventilator free time	3.2 ± 3.2	3.7 ± 4.1	0.482
ICU mortality	19 (41.3%)	41 (16.5%)	<0.001*

Close to recommended caloric and protein intake by EN assoc. with better outcomes in critically ill septic pts





Patients received a mean amount of 1,057 kcal/d (14.5 kcal/kg/day) and 49 g protein/day (0.7 g/kg/d) by EN alone.

Elke G., et al. Crit Care 2014; **18**(1): R29.

Close to recommended caloric and protein intake by EN assoc. with better outcomes in critically ill septic pts

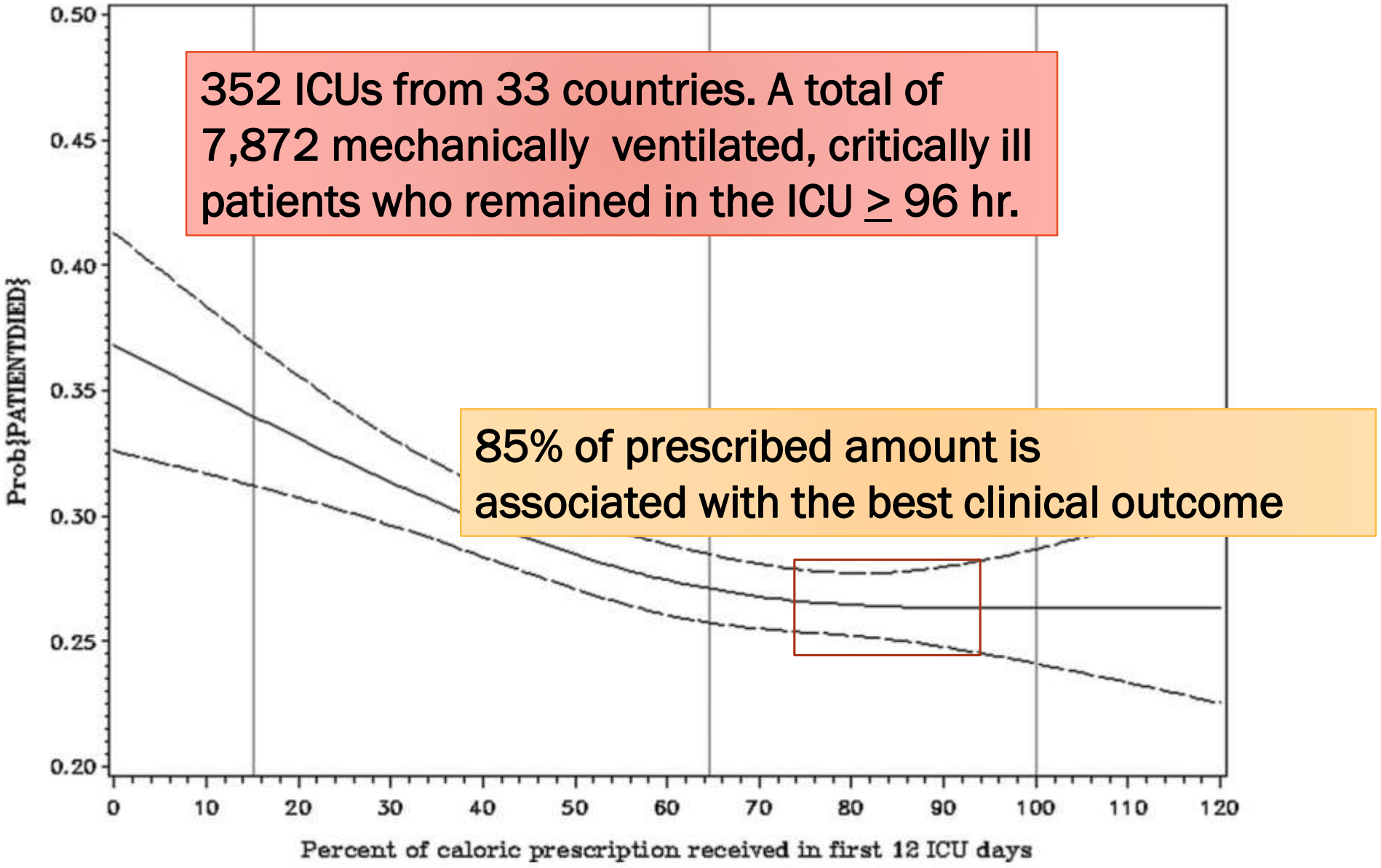
- 60-day mortality was 30.5% and patients were mechanically ventilated for median 8.4 days.
- An increase of 1,000 kcal was associated with
  - reduced 60-day mortality 39%;
  95% CI: 0.48-0.77, P < 0.001
  - more ventilator-free days 2.81 days,
  95% CI: 0.53-5.08, P = 0.02
- An increase of 30 g protein per day
  - reduced 60-day mortality 24%;
  95% CI: 0.65-0.87, P < 0.001
  - more ventilator-free days 1.92 days,
  95% CI 0.58-3.27, P = 0.005

Relationship between enteral nutrition (tertile groups) and 60-day mortality

	OR	95%CI	P-value
Energy intake, kcal/d			<0.001
< 865	1.59	1.22-2.07	
865-1294	1.00	0.79-1.28	
> 1294 (Reference)	1		
Protein intake, g/d			<0.001
< 39.5	1.64	(1.26-2.13)	
39.5-58.9	1.16	(0.91-1.48)	
> 58.9 (Reference)	1		

Elke G., et al. Crit Care 2014; **18**(1): R29.

Association Between 12-day Nutritional Adequacy and 60-Day Hospital Mortality



Heyland DK, et al. Crit Care Med. 2011 Dec;39(12):2619-26

Clinical Outcomes Related to Protein Delivery in Critically Ill Patients

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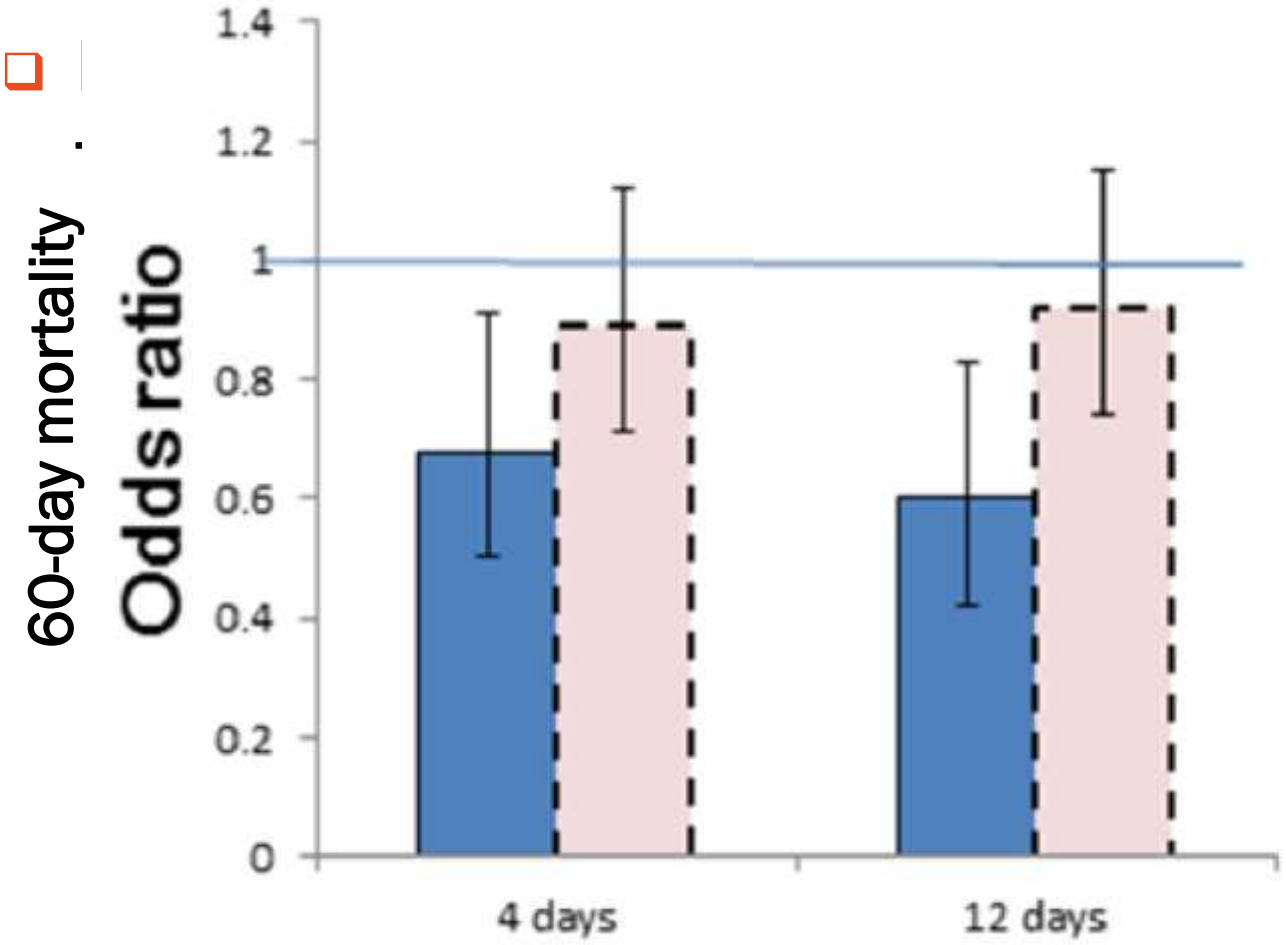


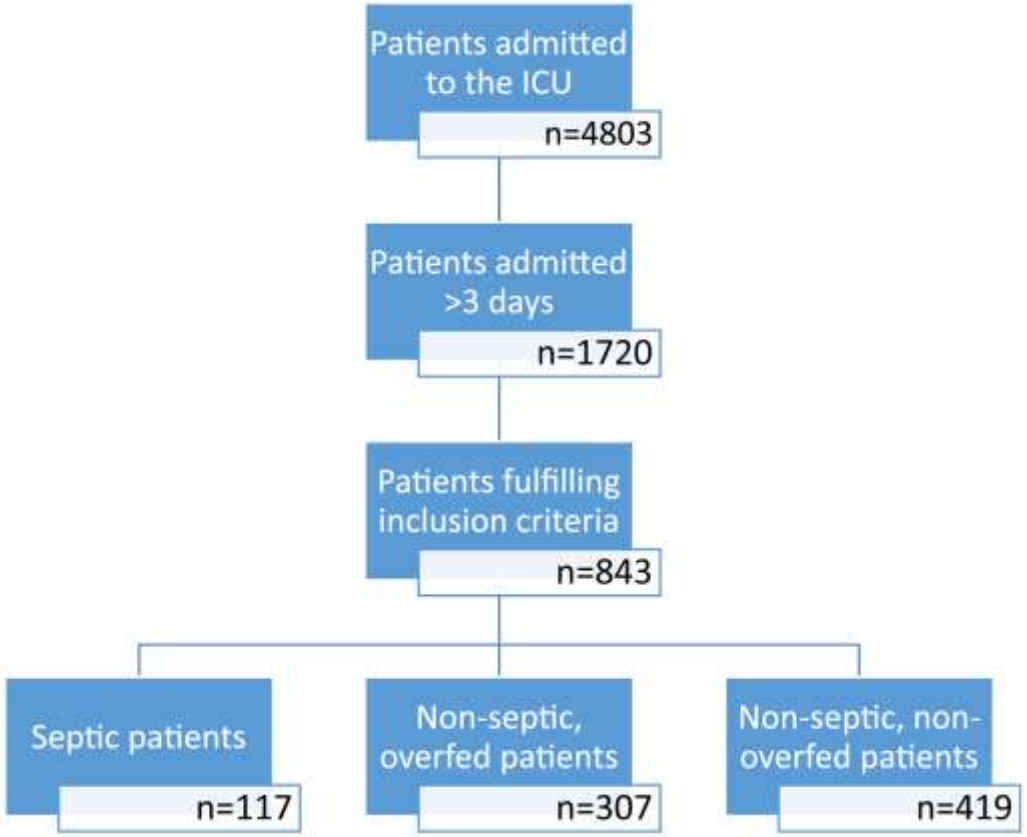
Practices in
3 (INS 2013)

Protein intake (mean daily delivery ≥80% of prescribed vs <80%)

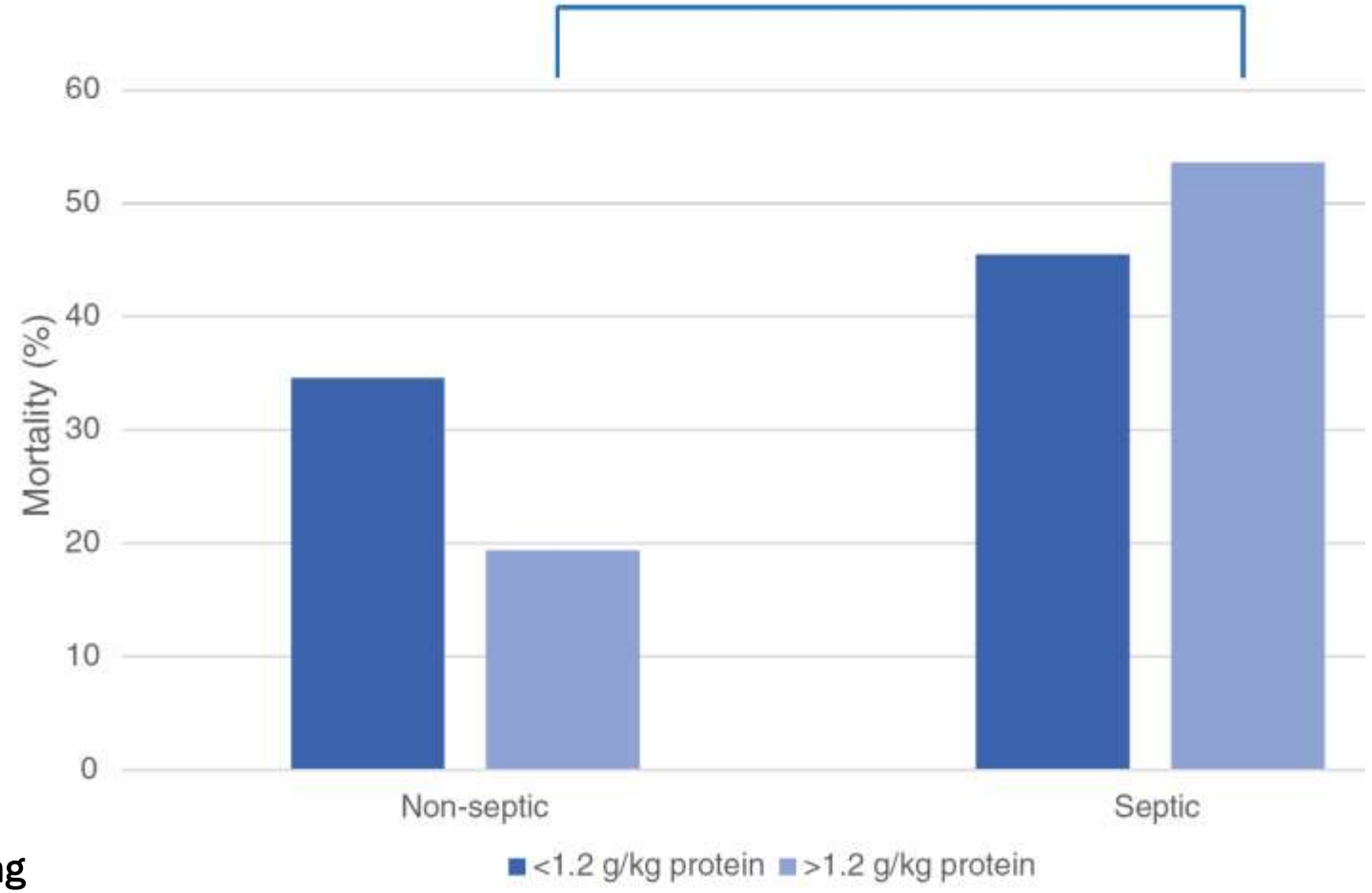
Energy intake (mean daily delivery ≥80% vs <80% of prescribed)

Nicolo M, et al. JPEN 2016;40(1):45-51.

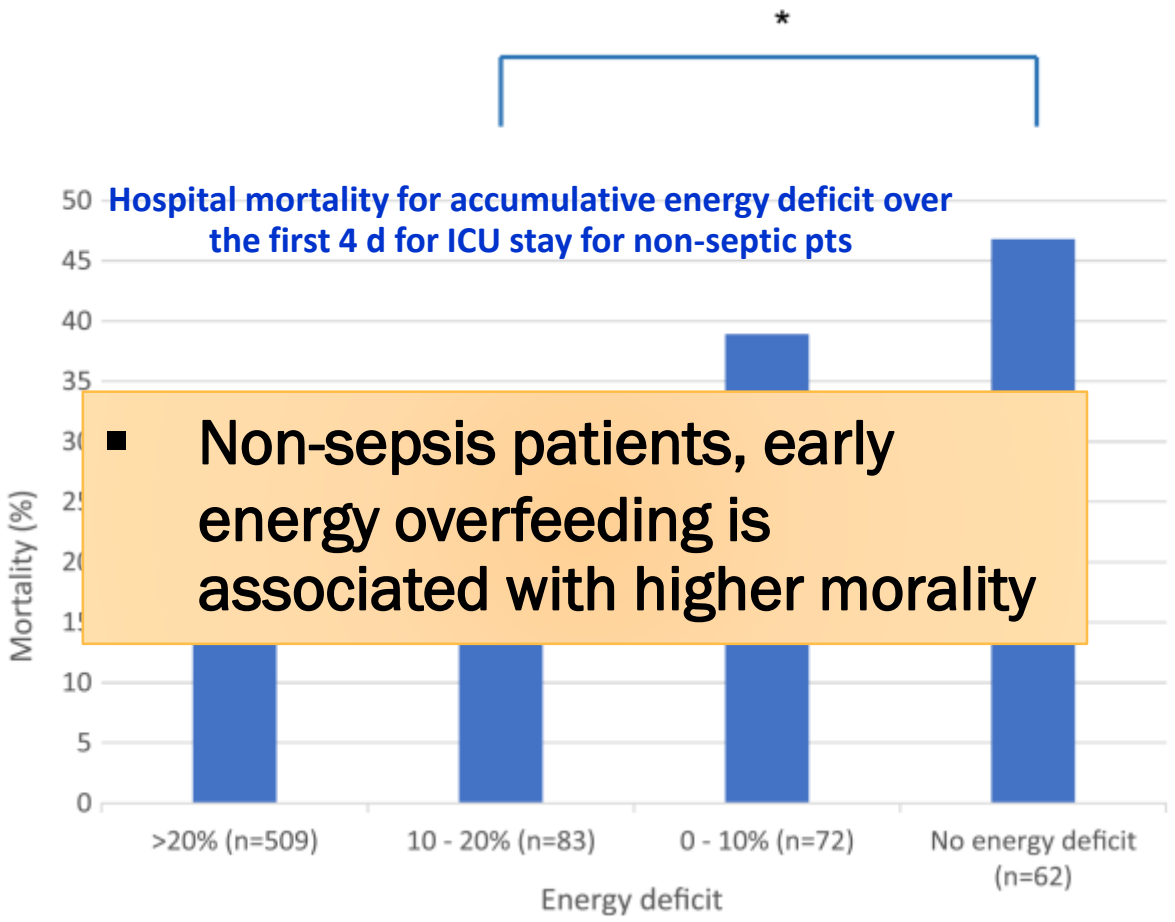
Early high protein intake is associated with low mortality and energy overfeeding with high mortality in non-septic mechanically ventilated critically ill patients



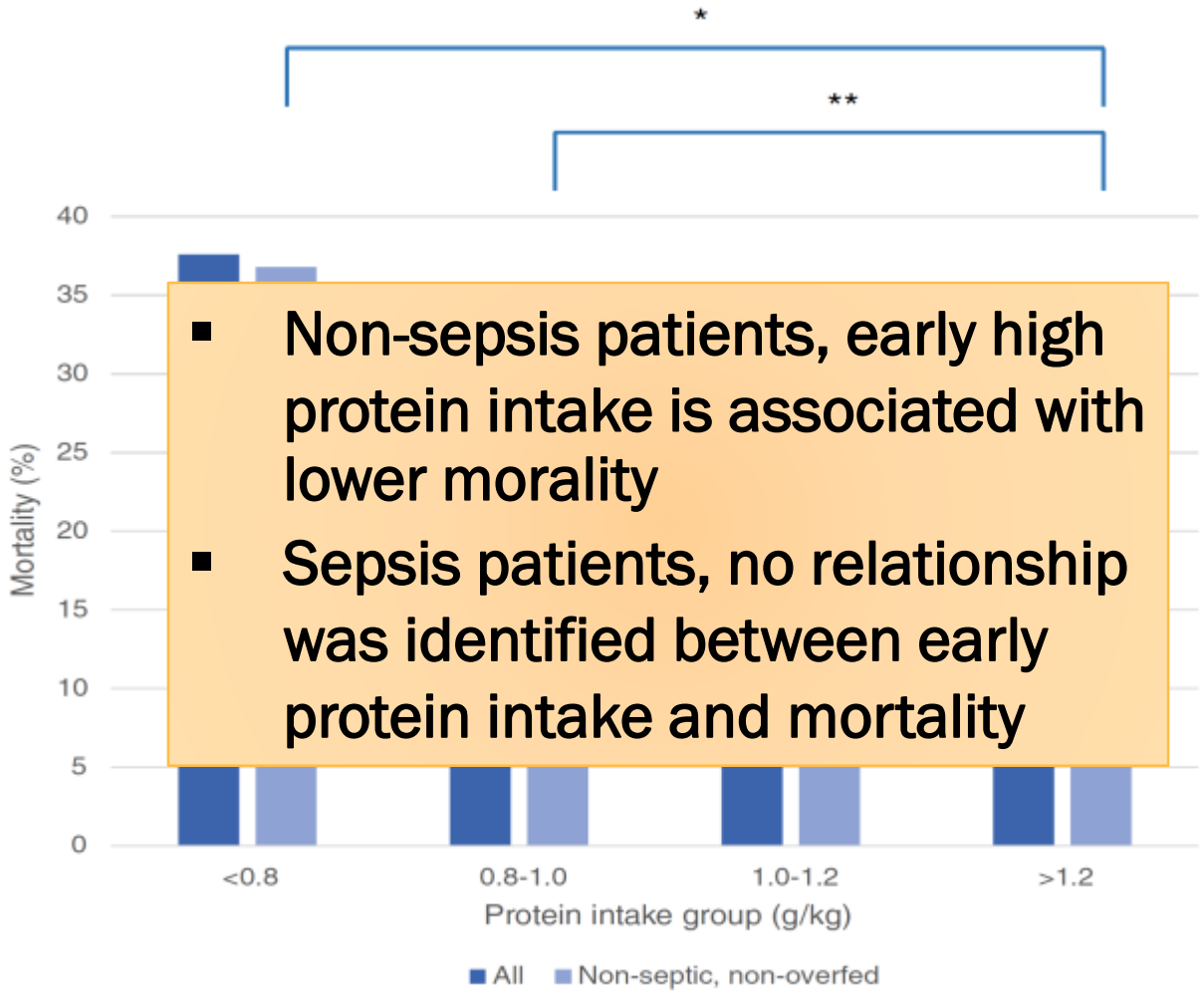
Energy on day 4
Ratio of energy intake/measure EE by IC >1.1 –overfeeding



Early high protein intake is associated with low mortality and energy overfeeding with high mortality in non-septic mechanically ventilated critically ill patients



- Non-sepsis patients, early energy overfeeding is associated with higher morality

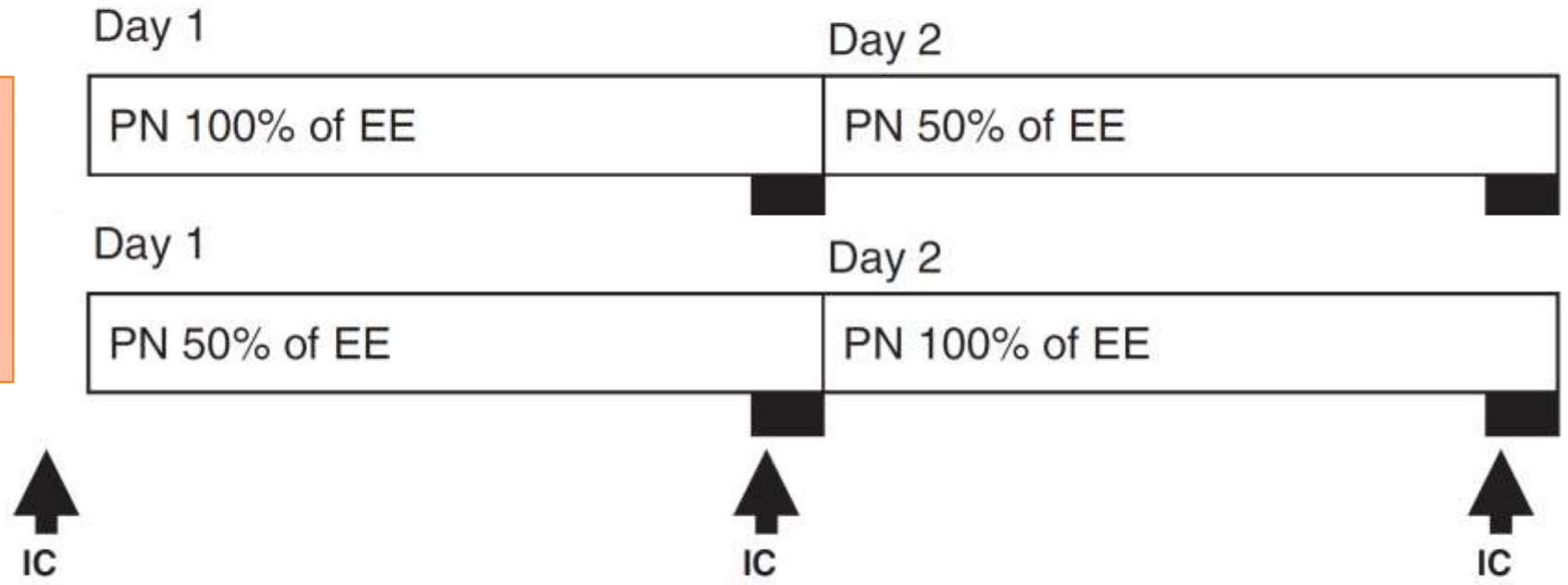


- Non-sepsis patients, early high protein intake is associated with lower morality
- Sepsis patients, no relationship was identified between early protein intake and mortality

Weijs P, et al. Crit Care. 2014;18(6):701.

Whole body protein kinetics during hypocaloric and normocaloric feeding in critically ill patients

Neurosurgical patients on MV (n = 16) were studied during a 48-h period.



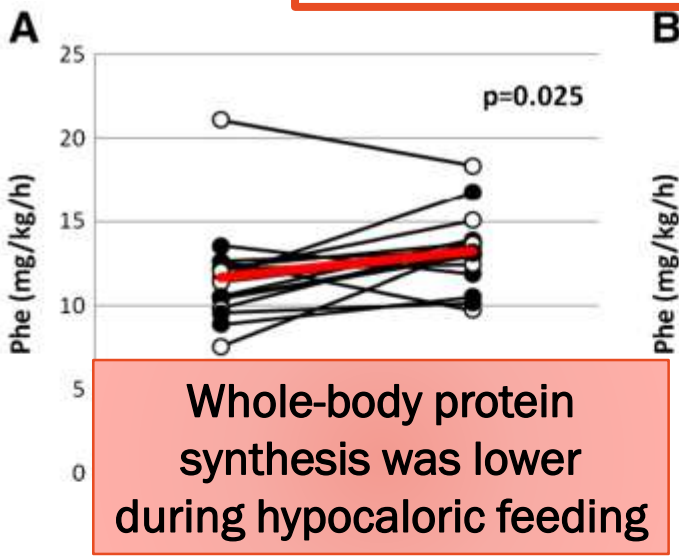
Pre-study
24.7 ± 3.3[a]
kcal/kg/24h

100% PN
24.5 ± 2.3[a]
kcal/kg/24h

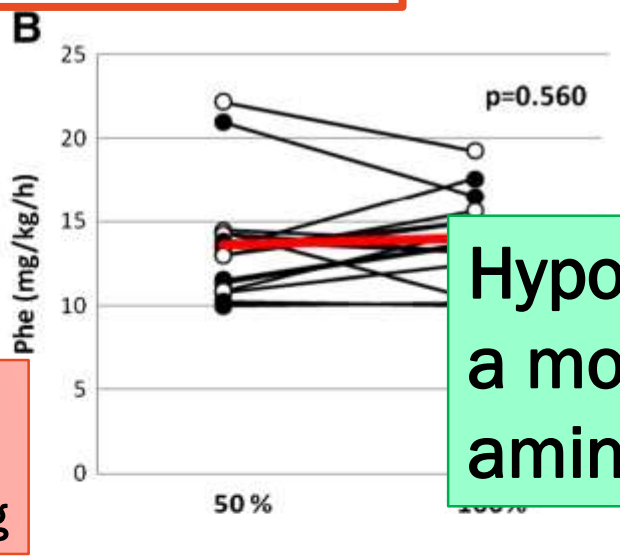
50% PN
23.4 ± 2.4[b]
kcal/kg/24h
(P = 0.049)

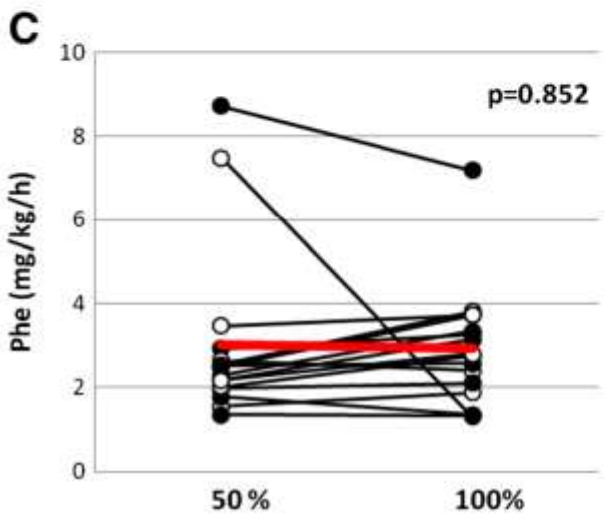
Berg A, et al. *Crit Care.* 2013;17(4):R158.

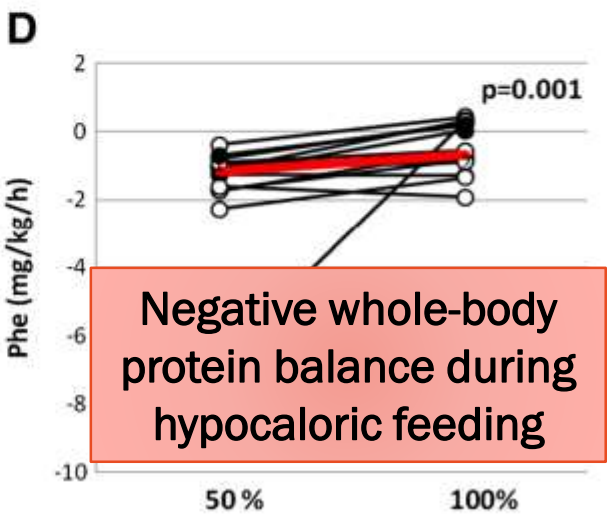
(A) Whole body protein synthesis;
(B) Whole-body protein degradation;
(C) Phenylalanine oxidation;
(D) Whole-body protein balance.



Whole-body protein synthesis was lower during hypocaloric feeding

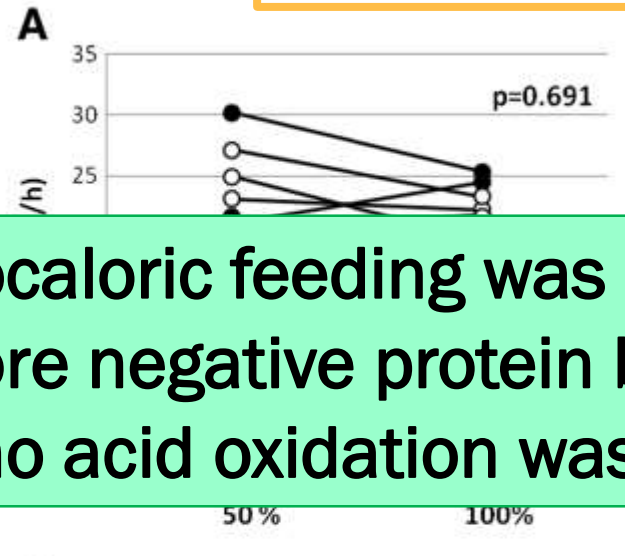


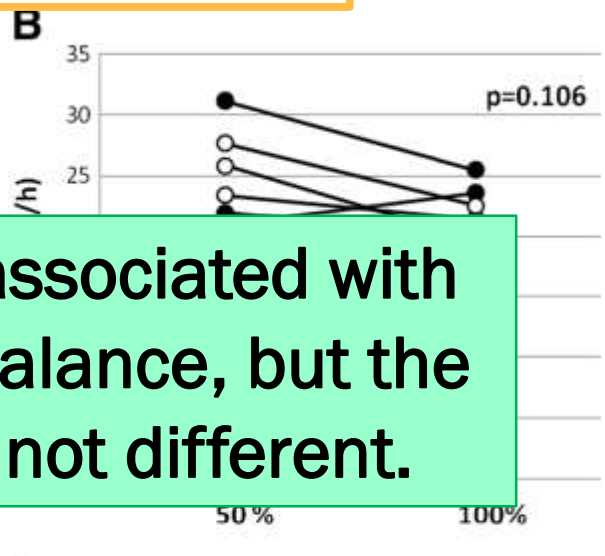




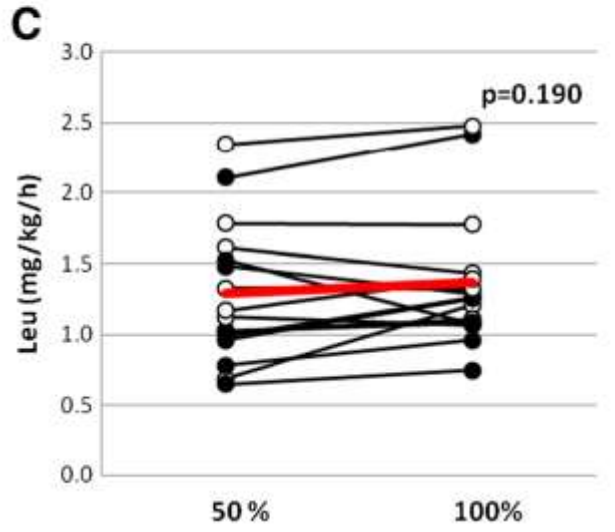
Negative whole-body protein balance during hypocaloric feeding

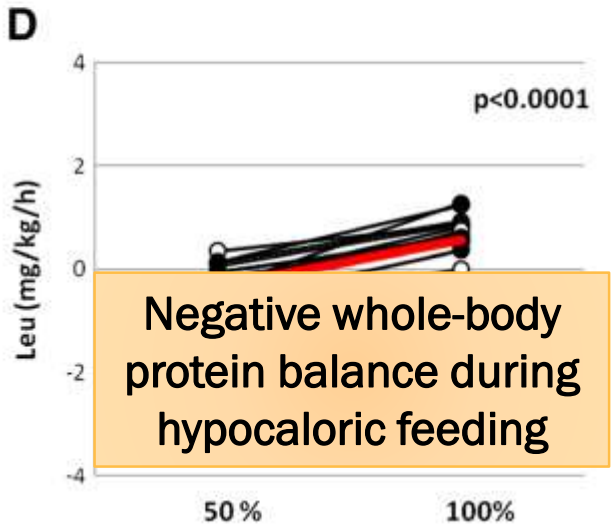
(A) Whole body protein synthesis;
(B) Whole-body protein degradation;
(C) Leucine oxidation;
(D) Whole-body protein balance.





Hypocaloric feeding was associated with a more negative protein balance, but the amino acid oxidation was not different.





Negative whole-body protein balance during hypocaloric feeding

Berg A, et al. *Crit Care.* 2013;17(4):R158.

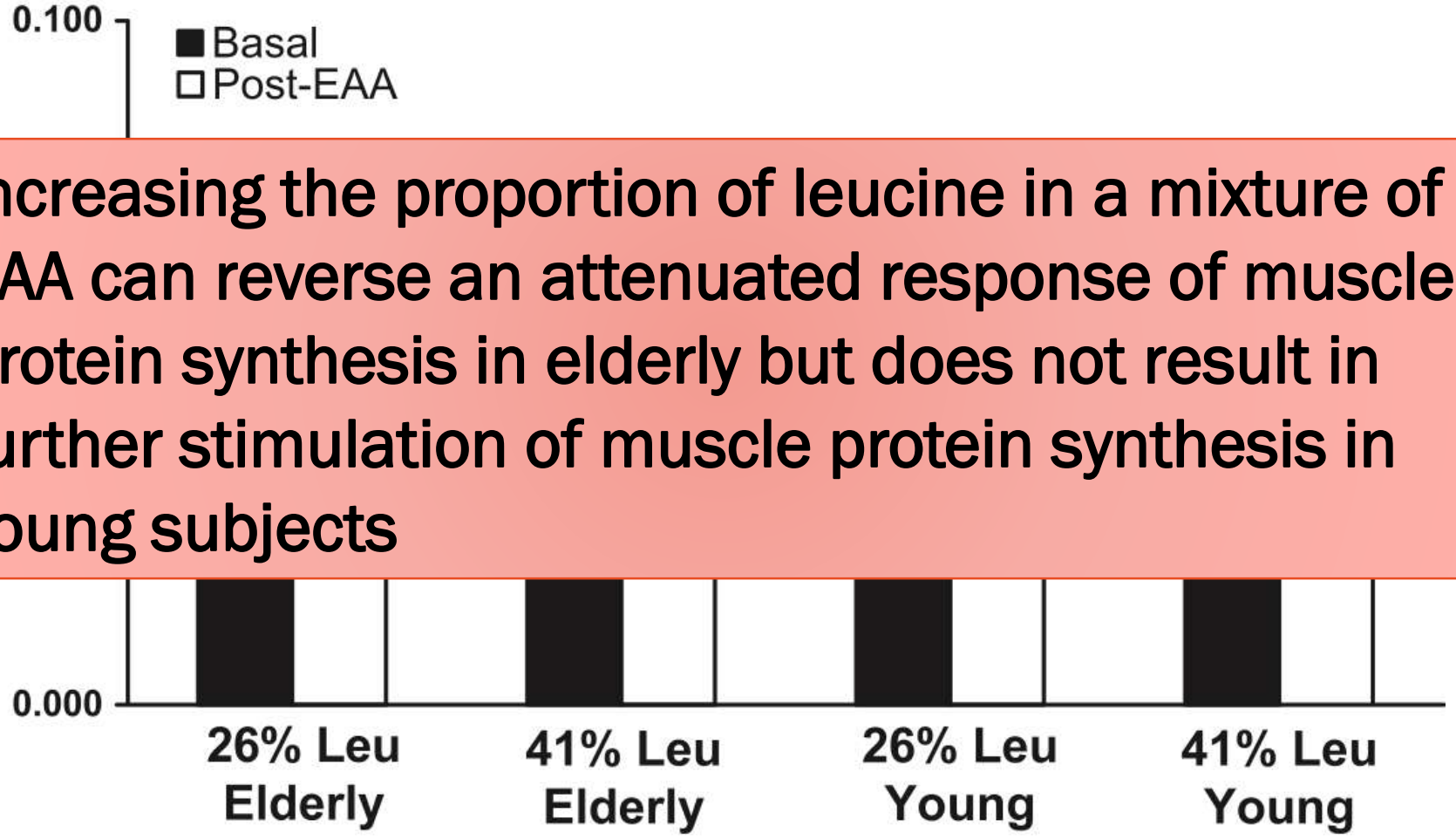
Anabolic resistance

- A state in which a patient is resistant to the normal stimulatory effect of AAs on muscle protein synthesis
  - Elderly – 1.4-2.5% muscle loss/y
  - Critically ill patients
  - Patients on bed rest
  - People exposed to weightless environment
- Splanchnic sequestration of AAs following feeding
  - Decrease the AAs available to muscles
- Insulin resistance
  - Limit AA uptake into muscles and hinder the maintenance of muscle protein
- Blunted responses to AAs with anabolic properties (Leucine)
  - Elderly required higher intake of EAAs compared to the young to generate the same acute response

A high proportion of leucine is required for optimal stimulation of the rate of muscle protein synthesis by essential amino acids in the elderly

Christos S. Katsanos, Hisamine Kobayashi, Melinda Sheffield-Moore, Asle Aarsland and Robert R. Wolfe

Am J Physiol Endocrinol Metab 291:E381-E387, 2006. First published 28 February 2006;
doi: 10.1152/ajpendo.00488.2005



Increasing the proportion of leucine in a mixture of EAA can reverse an attenuated response of muscle protein synthesis in elderly but does not result in further stimulation of muscle protein synthesis in young subjects

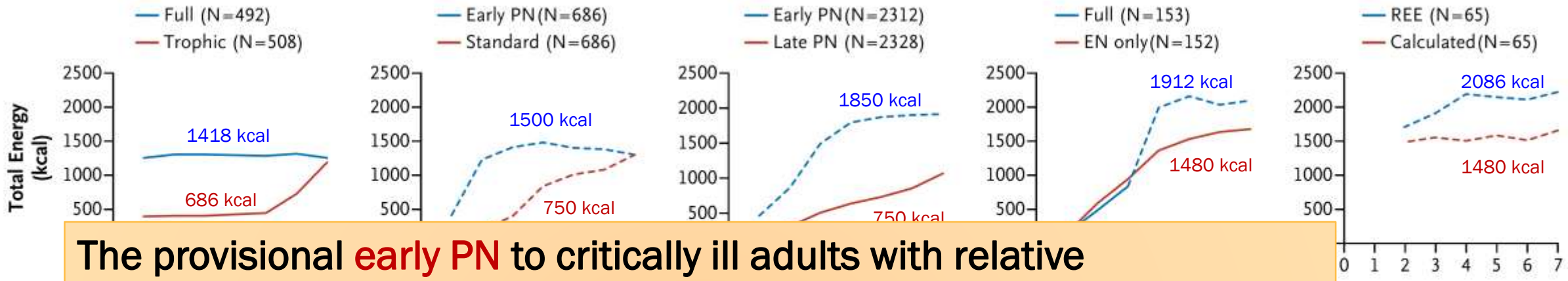
Early Trophic Enteral Nutrition Is Associated With Improved Outcomes in Mechanically Ventilated Patients With Septic Shock:
A Retrospective Review

- Single-center retrospective study of mechanically ventilated patients (n=66) admitted with septic shock patients receiving

	No EN	<600 kcal/d	≥600 kcal/d	*P* Value
Mortality, %				.64
DOMV (median da				
LOS (median days,				
Complications, %				.49
No feeding intolera				
Ileus				
Aspiration pneumo				
Nonocclusive mesenteric ischemia[c]	0	0	0	
Nonocclusive bowel necrosis[d]	0	0	0	

In patients with septic shock, those receiving <600 kcal/d EN within 48 hours had lower DOMV and LOS when compared to those who did not receive EN or those who received 600 kcal/d.

Patel JJ, et al. *J Intensive Care Med.* 2014. Oct 14. pii: 0885066614554887.



The provisional early PN to critically ill adults with relative contraindications to early EN, compared to standard care, did not result in difference in day-60 mortality.

When PN should be initiated? Still controversy

- Preexisting malnourished and EN is not feasible, PN should be administered ASAP
- Supplemental PN in case of EN failure after 3 days is a logical option but its beneficial impact remains to be established

					TICACOS (N=130)
Type of Patients					Mixed medical and surgical
New Infections in IC					More with REE
Duration of Mechar Ventilation					Longer with REE
Length of Stay in ICU	Unaffected	Unaffected	Longer with early PN	Unaffected	Longer with REE
Mortality in ICU	Unaffected	Unaffected (60-day mortality: unaffected)	Unaffected	Unaffected	Unaffected (trend toward reduced hospital mortality)

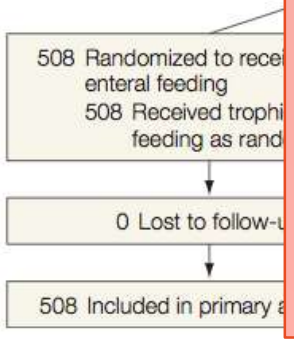
Casaer MP, Van den Berghe G. N Engl J Med. 2014;370(13):1227-36.

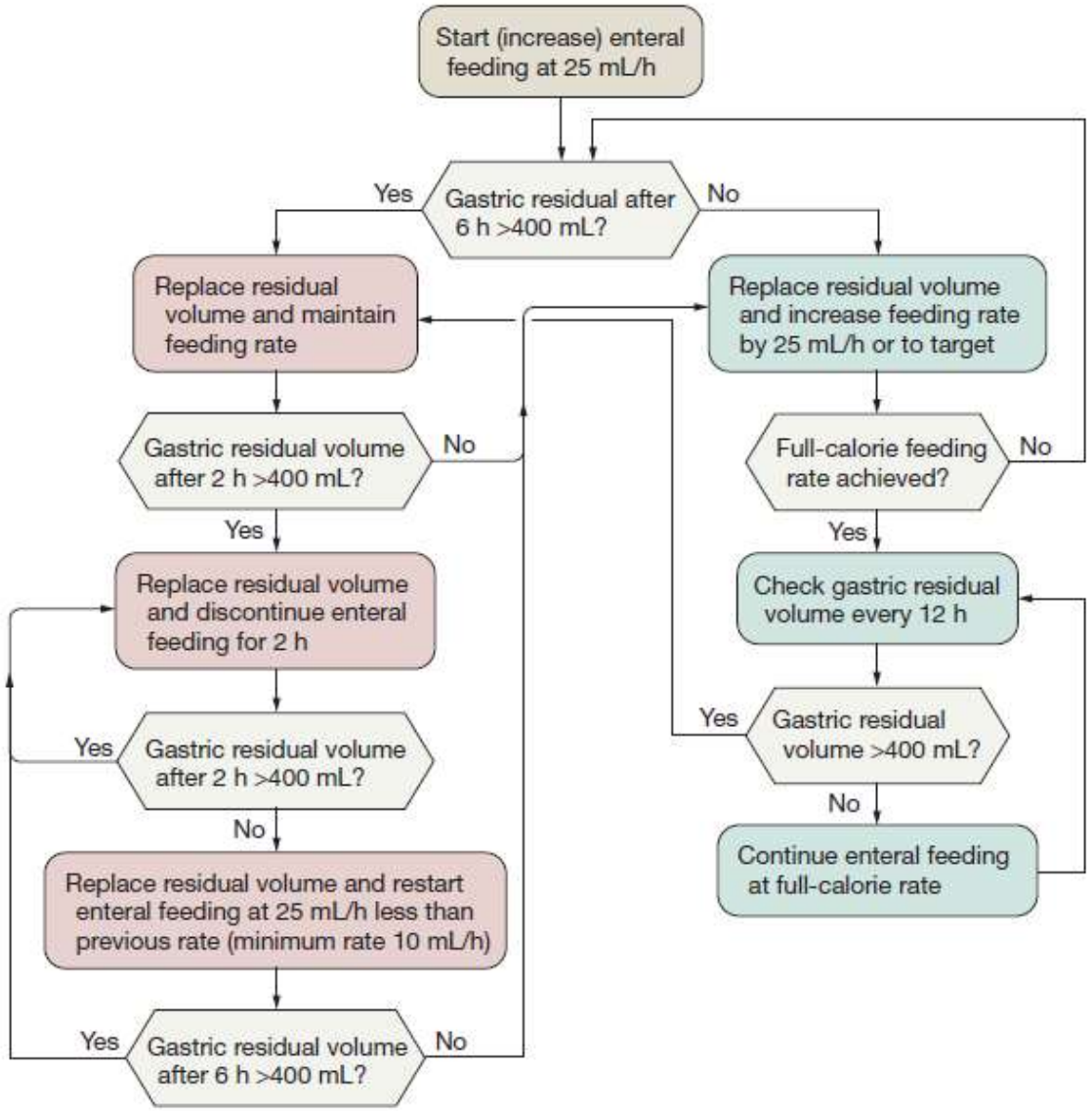
ONLINE FIRST

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

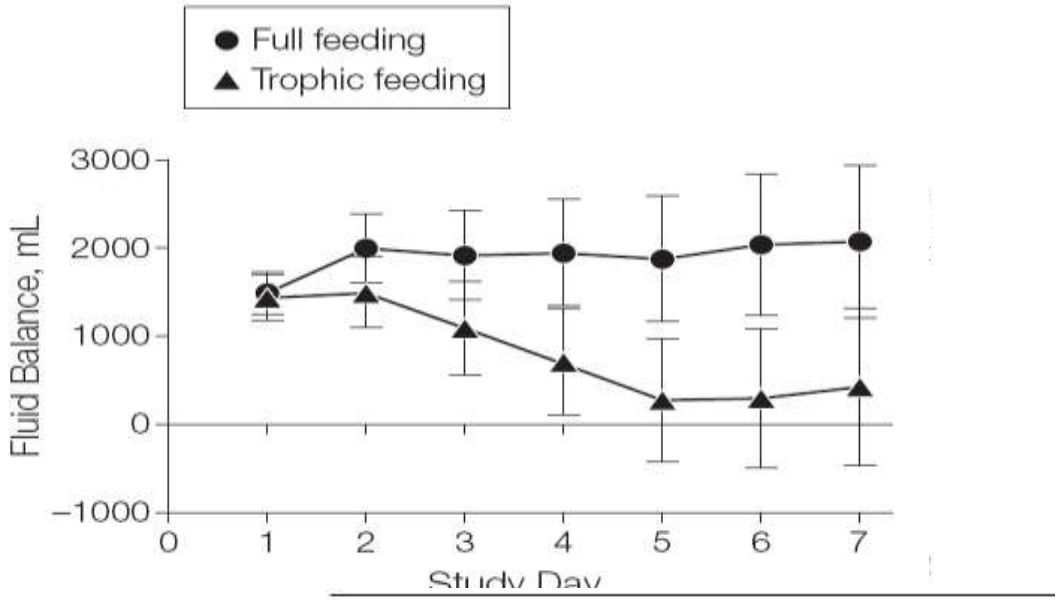
The EDEN Randomized Trial

- full-energy feeding:
  - N=492
  - EN initiated at 25 mL/hr.
  - Target 25–30 kcal/kg of predicted BW/day of NPC
  - 1.2–1.6 g/kg of predicted BW/day of protein
- trophic group
  - N=508
  - EN initiated at 10 mL/hr. (in first 272 pts) then increased to 20 mL/hr
  - Advance to full-energy target after 144 hrs (Day 6)





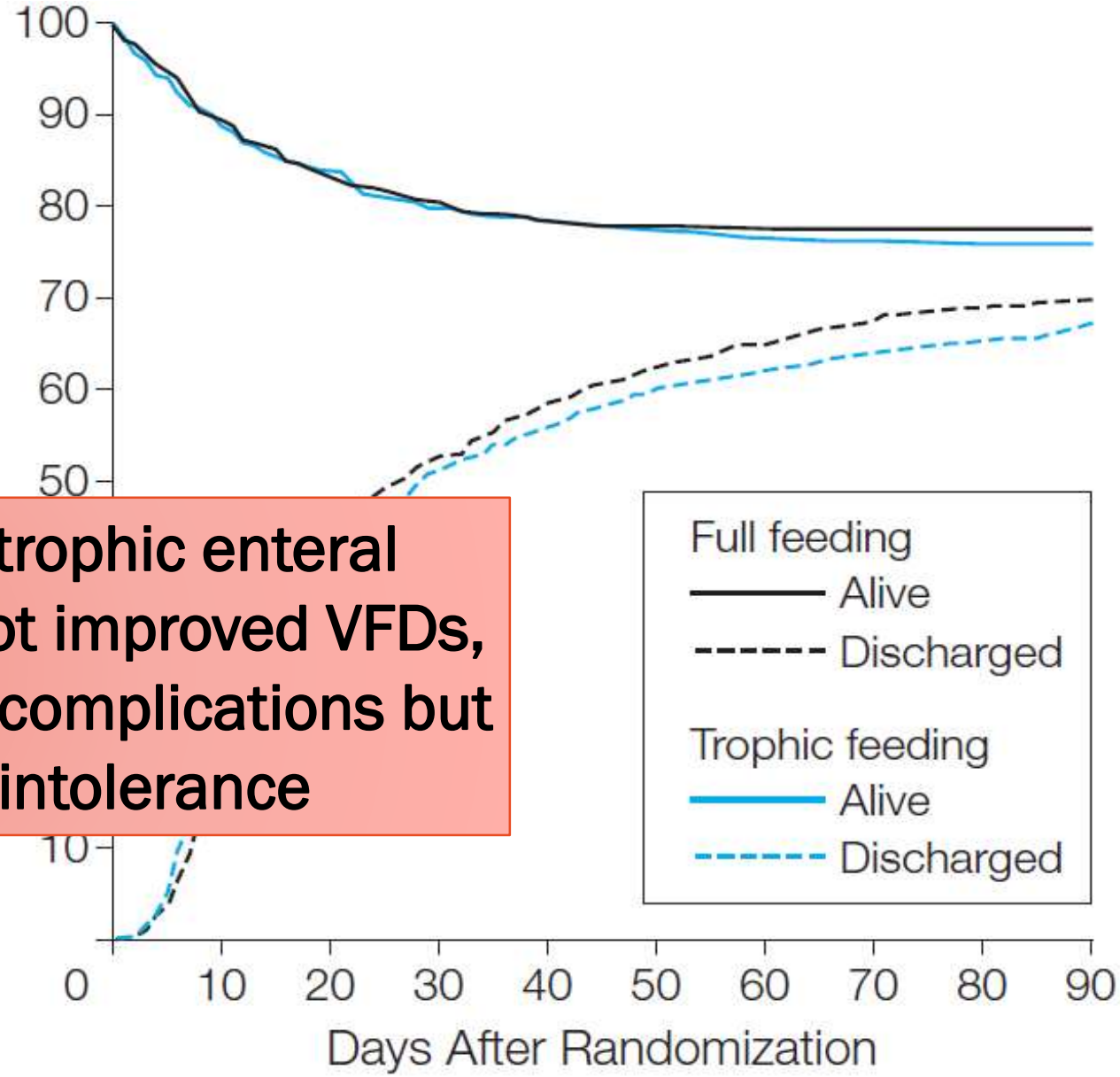
Rice TW, Wheeler AP, Thompson BT, et al. *Jama.* Feb 22 2012;307(8):795-803.



No. of patients
Full feeding
Trophic feed

In patients with ALI, initial trophic enteral feeding for up to 6 days did not improved VFDs, 60-day mortality or infectious complications but was associated with GI intolerance

60-d mortality, No. (%) [95% CI]	
Development of infections, No. (%) [95% CI]	
VAP	
Clostridium difficile colitis	
Bacteremia, No. (%)	



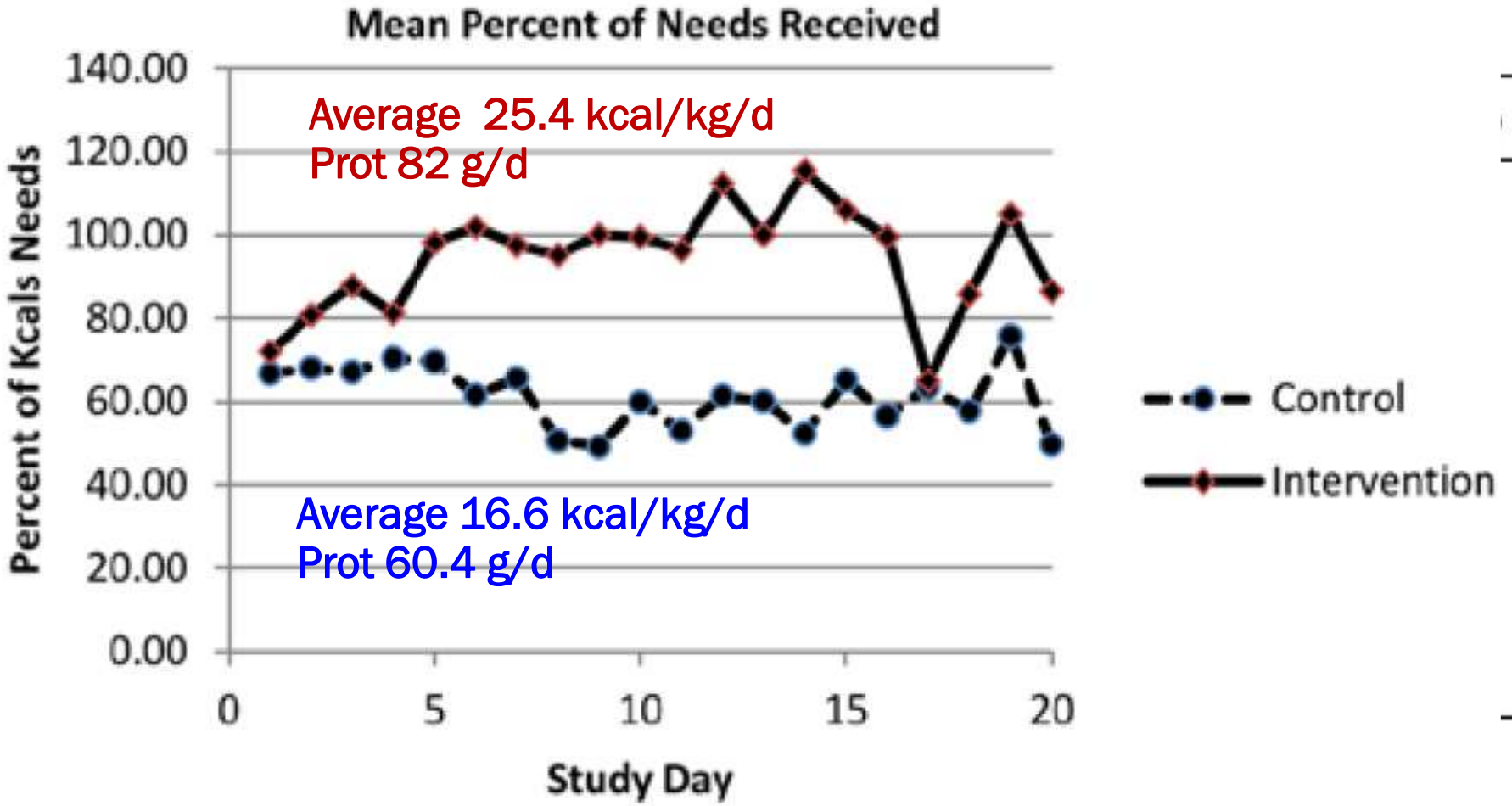
Intensive Nutrition in Acute Lung Injury: A Clinical Trial (INTACT)

Variable	Intervention (n = 40)	Control (n = 38)	*P* Value
Age, y	52.5 (17.1)	58.6 (16.2)	.11
Female, n (%)	21 (51.2)	17 (44.7)	.56
Race, n (%)			.88
African American	10 (25)	11 (29)	
Caucasian	22 (55)	18 (47)	
Hispanic	8 (20)	9 (24)	
Height, cm	170.1 (10.5)	170.7 (10.1)	.81
Weight, kg	86.3 (27.6)	88.6 (27.2)	.71
Body mass index, kg/m^2	29.8 (9.3)	30.1 (8.9)	.89
BMI ≥30, n (%)	18 (45)	18(47)	.83
SGA category, n (%)			.15
Normal	27 (65.8)	23 (60.5)	
Moderate	11 (26.8)	15 (39.5)	
Severe	3 (7.3)	0	
Baseline SOFA	9.3 (3.8)	9.4 (3.4)	.97
APACHE II	23.4 (9.3)	27.7 (7.9)	.03
PaO_2:FiO_2 ratio	195 (105)	183 (122)	.69
PaO_2:FiO_2 ratio ≤200, n (%)	23 (58)	21 (55)	.84
CRP, mg/dL	102.2 (92.2)	131.2 (92)	.20
White blood cell count, cells × 10^9/L	13.3 (12.2)	11.1 (6.2)	.34
Glucose, mg/dL	154 (48.9)	150.9 (55.1)	.78

Braunschweig CA, et al. JPEN. 2015;39(1):13-20.

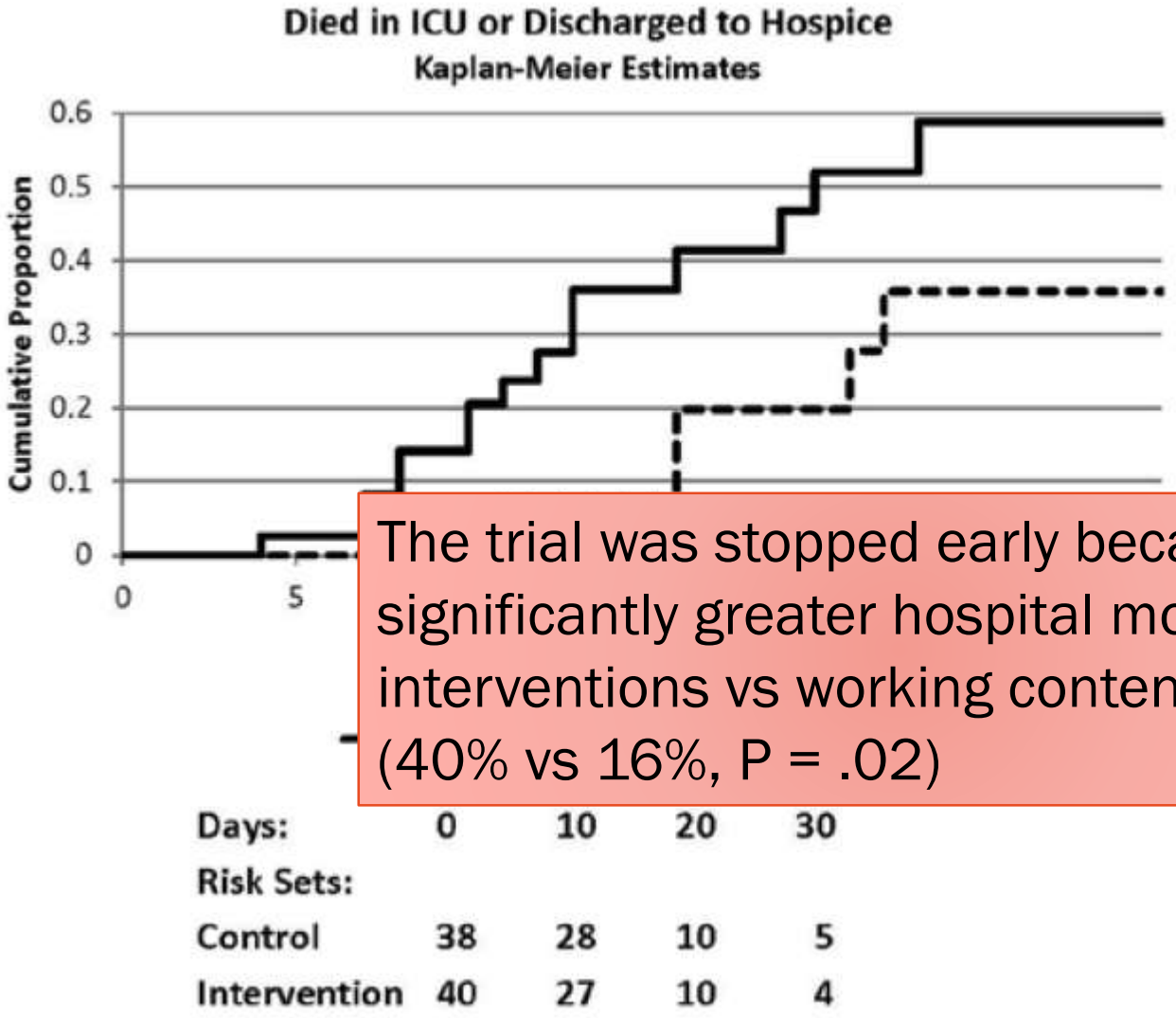
Intensive Nutrition in Acute Lung Injury: A Clinical Trial (INTACT)

Variable	*P* Value
Estimated energy n	.48
Estimated protein r	.59
Energy received/d,	<.0001
Percentage of estin	<.0001
kcal/kg received pe	<.0001
Received PN, n (%	.42
Mean days of PN i	.89
Protein received pe	<.0001
Percentage of estin	<.0001
Received parentera	.09



Braunschweig CA, et al. JPEN. 2015;39(1):13-20.

Intensive Nutrition in Acute Lung Injury: A Clinical Trial (INTACT)



The trial was stopped early because of significantly greater hospital mortality in interventions vs working content (40% vs 16%, P = .02)

IMNT (n = 40)	SNSC (n = 38)	*P* Value
27.2 (18.2)	22.8 (14.3)	.33
15.5 (12.8)	16.1 (11.5)	.83
8.8 (8.7)	6.4 (6.6)	.17
6 (4–10)	7 (3–14)	.85
5 (12)	8 (21)	.29
30 (73)	26 (68)	.64
(3.0)	2.4 (4.0)	.85
(29.3)	11 (28.9)	.98
(0.6)	0.9 (0.7)	.08
(47.6)	14 (23.6)	.25
(70.4)	35.9 (27.9)	.03
16 (40.0)	6 (15.8)	.017

Braunschweig CA, et al. JPEN. 2015;39(1):13-20.

Normocaloric vs. hypocaloric feeding on the outcomes of ICU patients:
a systematic review and meta-analysis

- 6 studies (n=2517). The mean age and BMI across the studies were 53 ± 5 years and 29.1 ± 1.5 kg/m2, respectively.
  - 2 studies: normocaloric feeding (77% of goal) vs trophic feeding (20% of goal),
  - 4 studies: normocaloric feeding (72% of goal) vs permissive underfeeding (49% of goal).
- No significant difference in
  - the risk of infectious complications(OR 1.03; 95 % CI 0.84–1.27, I^2= 16 %),
  - hospital mortality (OR 0.91; 95 % CI 0.75–1.11, I^2= 8 %)
  - ICU LOS (mean difference 0.05 days; 95 % CI 1.33–1.44 days; I^2= 37%)
  - VFDs (in 3 studies) with no significant difference between the normocaloric and intentional hypocaloric groups

Marik PE, et al. Intensive Care Med. 2016;42(3):316-323.

Normocaloric vs. hypocaloric feeding on the outcomes of ICU patients:
a systematic review and meta-analysis

Author	Year	Setting	Patients[a]	*n*	Time[b]	Age		BMI (kg/m^2)		APACHE II		Caloric goal	
						St	Hypo	St	Hypo	St	Hypo	St	Hypo
Trophic													
Rice	2011	Single center	MV >3 days	200	<24	54	53	28.2	29.2	27	27	25–30 kcal/kg/day	300 cals/day
Rice	2012	Multicenter	Acute lung injury	1000	<48	52	52	30.4	29.9	–	–	25–30 kcal/kg/day	300 cals/day
Permisssive underfeeding													
Arabi	2011	Single center	ICU >2 days; 99 % MV	240	<24	52	50	28.5	28.5	25	25	90–100 % goal	60–70 % goal
Charles	2014	Single center	SICU >2 days	83	–	53	50	28.1	32.9	17	17	25 kcal/kg/d	12.5–15 kcal/kg/day
Petros	2014	Single center	ICU >3 days	100	<24	64	67	27.1	28.6	27	30	100 % goal[c]	50 % goal
Arabi	2015	Multicenter	ICU >3 days; 97 % MV	894	<24	51	50	29.7	29.0	21	21	70–100 % goal	40–60 % goal

Marik PE, et al. Intensive Care Med. 2016;42(3):316-323.

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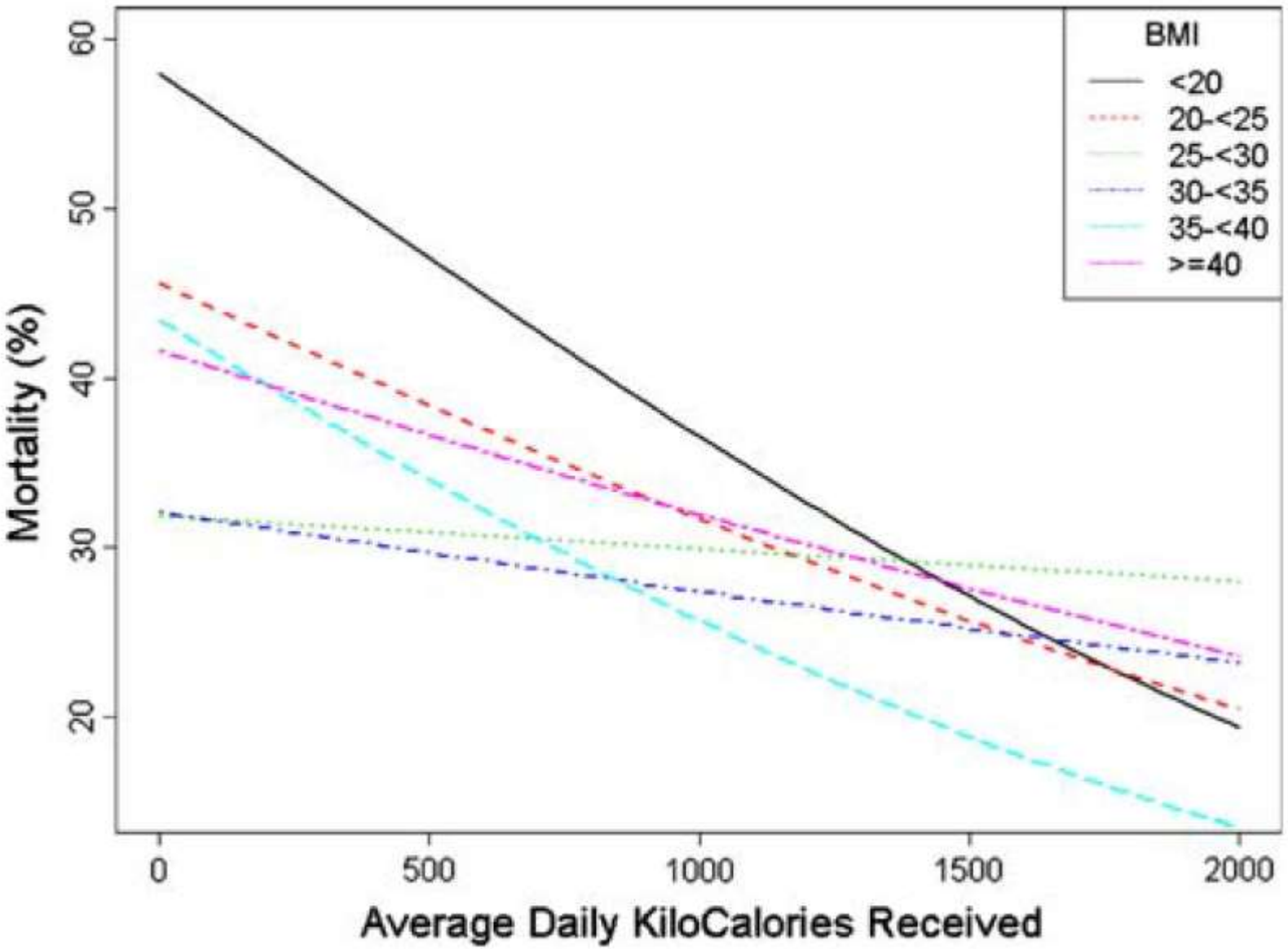
Author	Kilocalories/goal (%)		Protein (g)		VFD		ICU LOS		Hospital mortality (%)	
	St	Hypo	St	Hypo	St	Hypo	St	Hypo	St	Hypo
Trophic										
Rice	1418/75	300/16	54	11	18	18	7.6 ± 5.9	8.1 ± 6.1	19.6	22.4
Rice	1300/80	400/25	–	–	15	15	11.0 ± 9.8	11.3 ± 10.6	22.2	23.2[d]
Permissive underfeeding										
Arabi	1102/71	915/59	43	47	–	–	14.5 ± 15.5	5 11.7 ± 8.1	42.5	30
Charles	1338/–	982/–	83	86	–	–	13.5 ± 7.1	16.7 ± 17.2	9.5	7.3
Petros	19.7[c]/75	11.3[c]/42	–	–	–	–	–	–	22.2	21.7
Arabi	1299/71	835/46	59	57	75[a,b]	77	13[a]	13	27.6	24.2

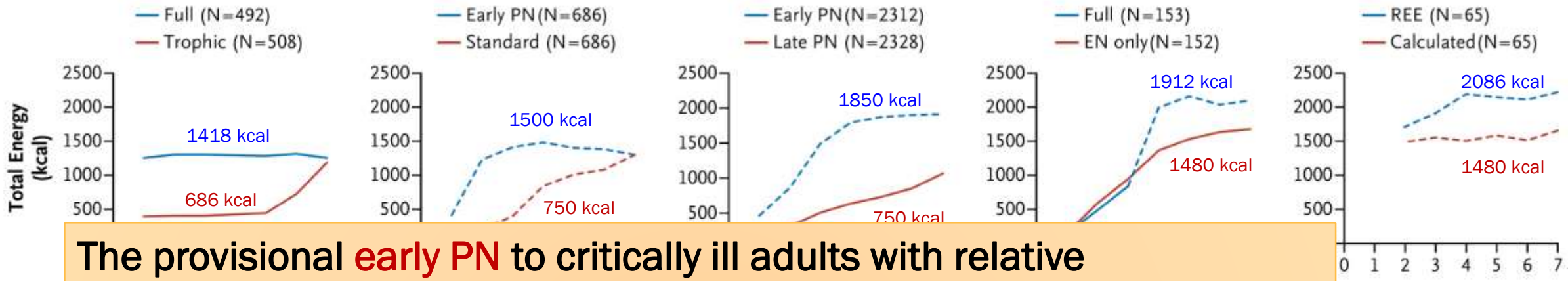
Marik PE, et al. Intensive Care Med. 2016;42(3):316-323.

Nutritional intake and outcomes in critically ill patients



An increase of 1,000 kcal/d was assoc. with
- 26% reduction of 60-day mortality
- an increased 3.5 VFDs

Alberda C. Intensive Care Med 2009;35:1728-37



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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 30, 2014 VOL. 371 NO. 18

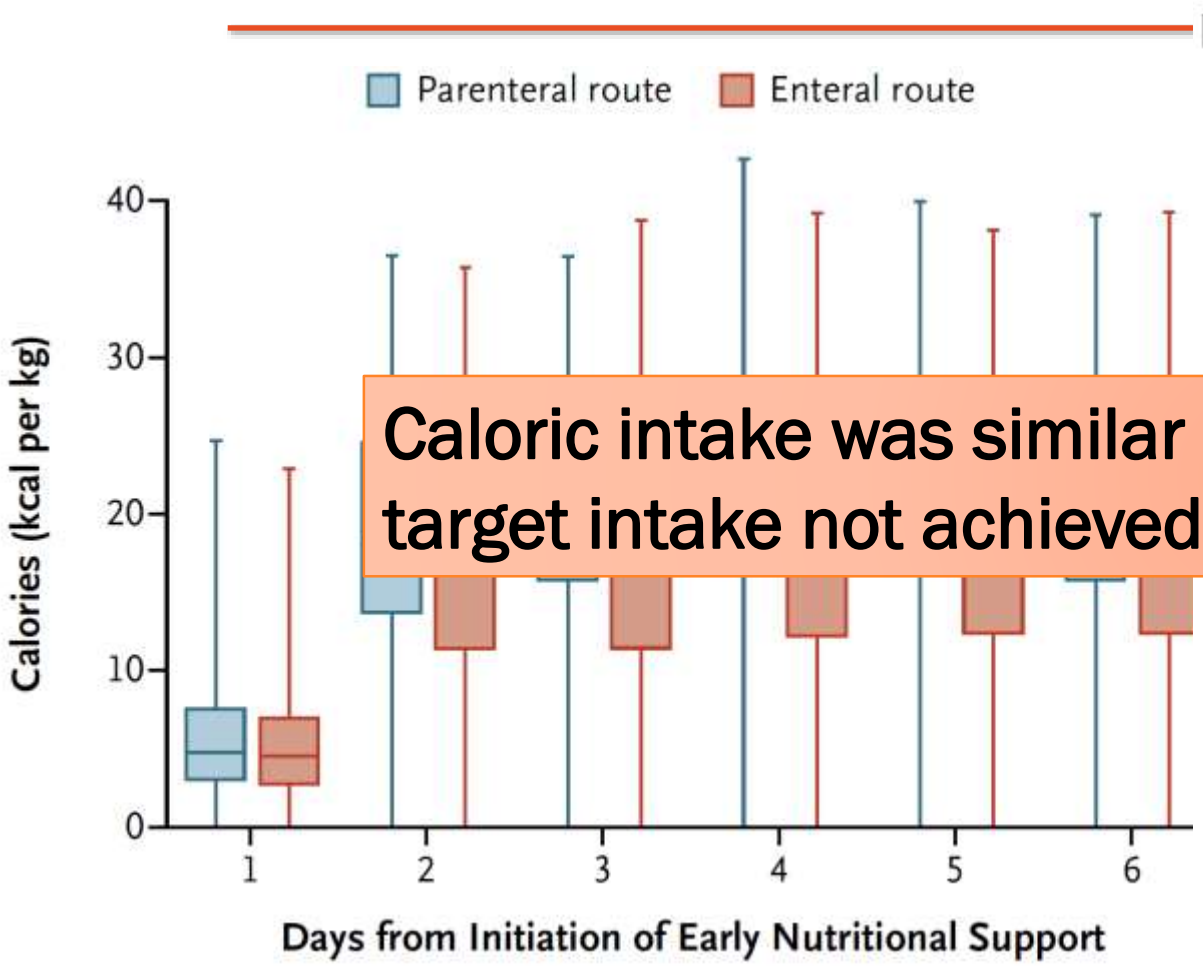
Trial of the Route of Early Nutritional Support in Critically Ill Adults

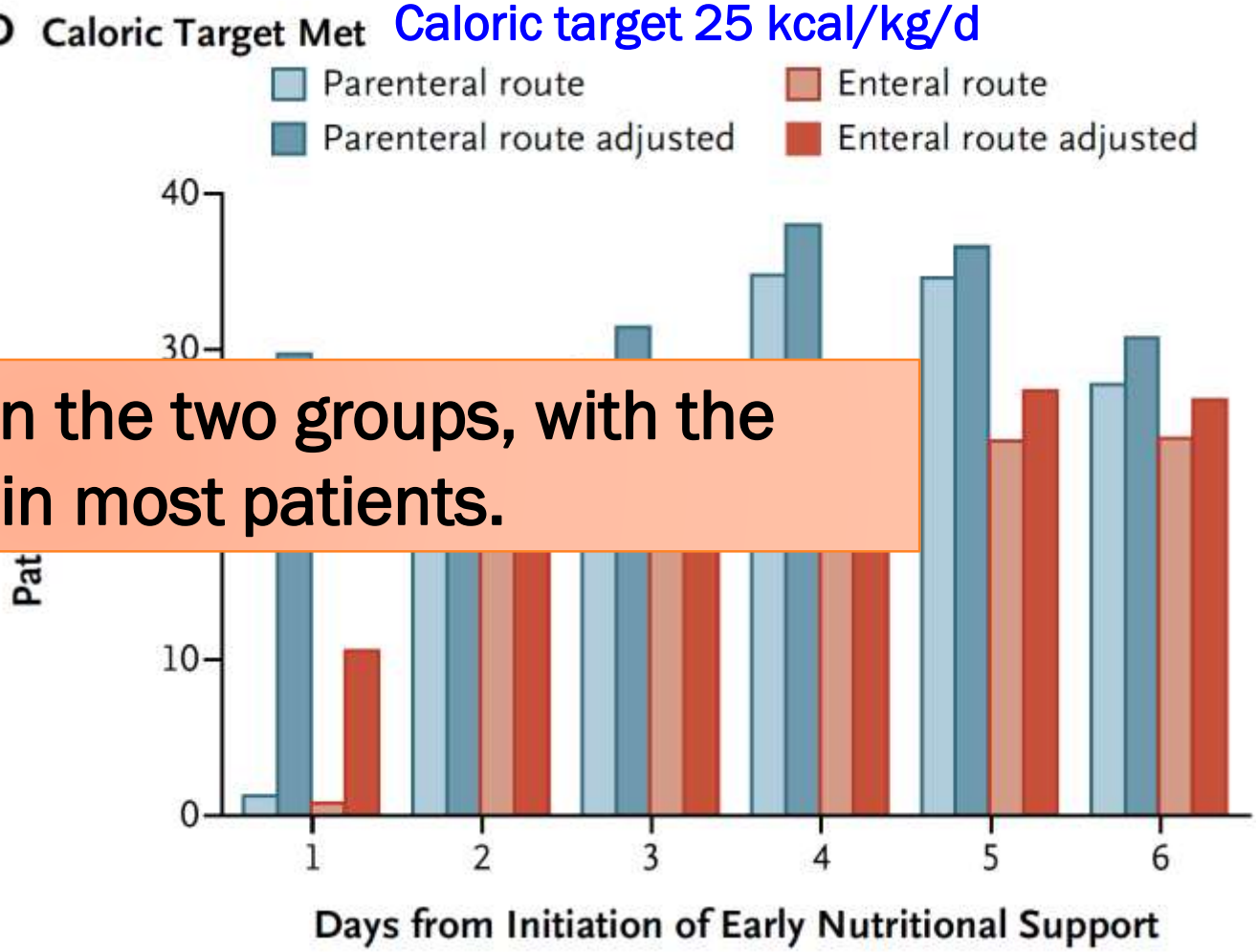
Sheila E. Harvey, Ph.D., Francesca Parrott, M.Sci., David A. Harrison, Ph.D., Danielle E. Bear, M.Res., Ella Segaran, M.Sc., Richard Beale, M.B., B.S., Geoff Bellingan, M.D., Richard Leonard, M.B., B.Chir., Michael G. Mythen, M.D., and Kathryn M. Rowan, Ph.D., for the CALORIES Trial Investigators*

- Pragmatic RCT in 33 ICUs in England
- Early EN (n=1197) vs Early PN (n=1191) within 36 h of admission and continue for up to 5 d according to local products and policies
- Hypothesis: The parenteral route is superior to the enteral route for the delivery of early nutritional support in adults who had an unplanned admission to ICU and who could be fed through either route.

Harvey SE, et al. *N Engl J Med.* 2014;371(18):1673-1684.

The CALORIES Trial





Caloric target 25 kcal/kg/d

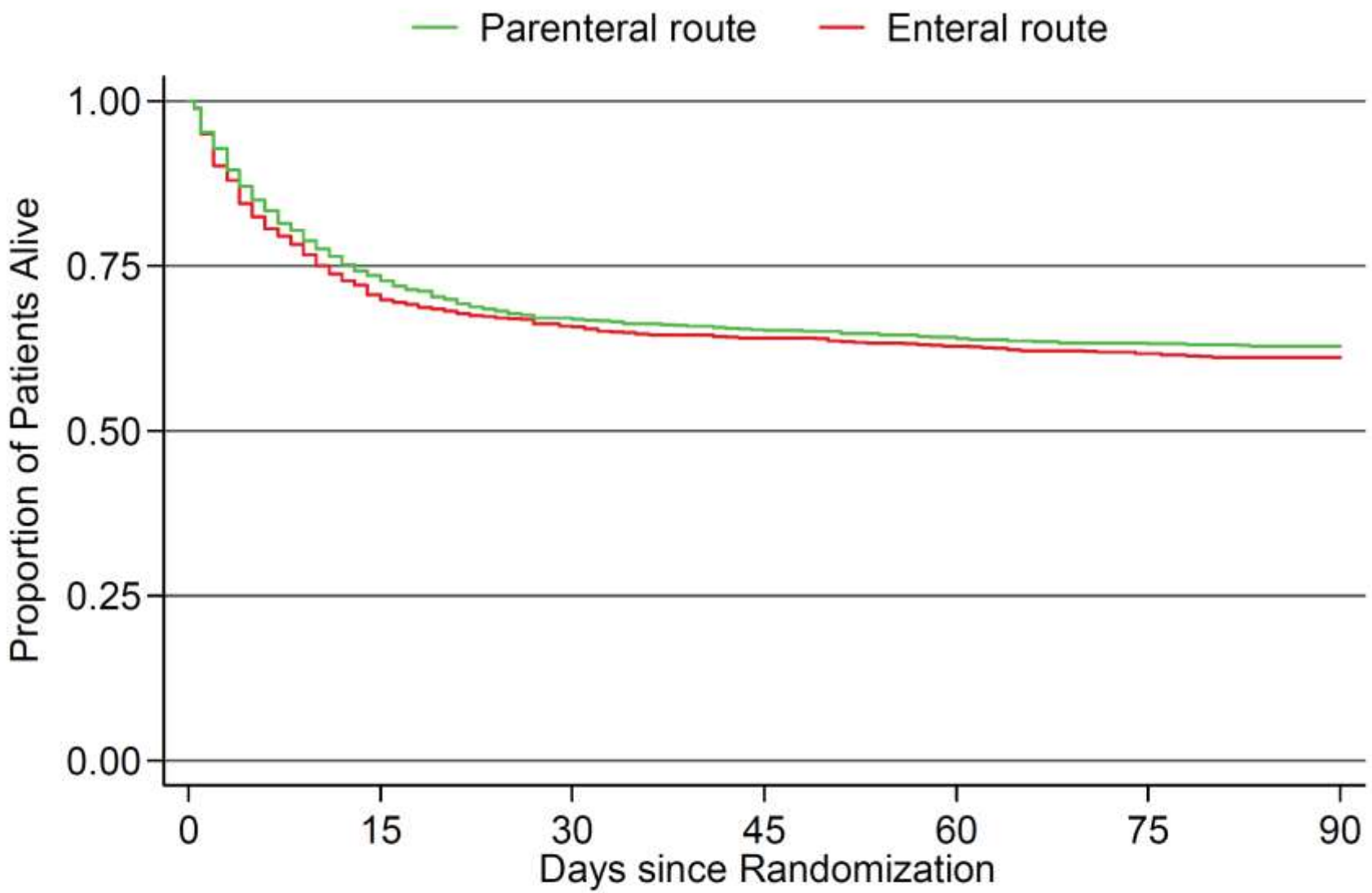
Caloric intake was similar in the two groups, with the target intake not achieved in most patients.

Harvey SE, et al. *N Engl J Med.* 2014;371(18):1673-1684.

The CALORIES Trial

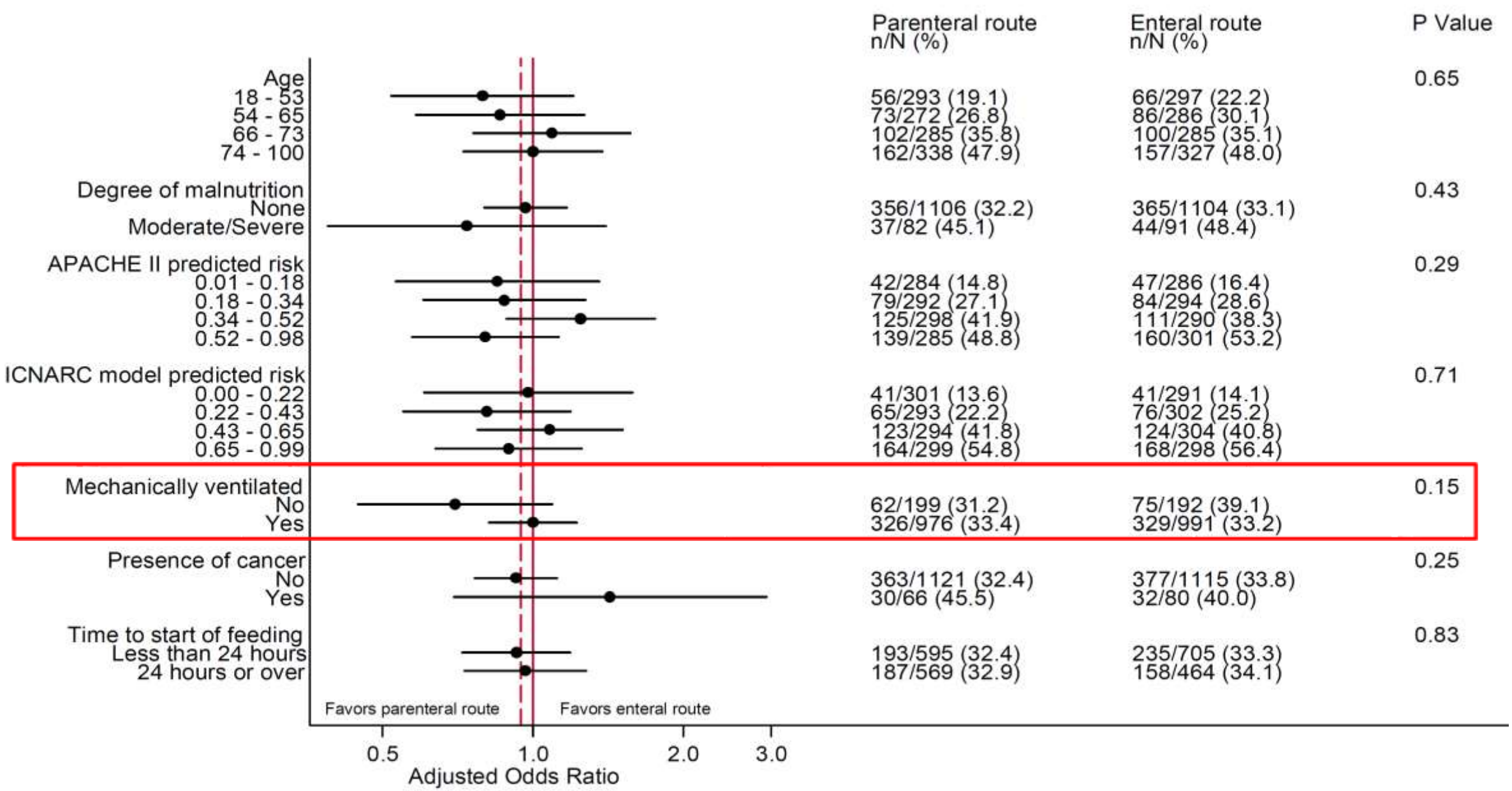
	Early EN	Early PN		P
30-d mortality	409 (34.2%)	393 (33.1%)	RR 0.97 95% CI 0.86 to 1.08	0.57
90-d mortality	464 (39.1%)	442 (37.3%)	RR 0.96 95% CI, 0.86 to 1.06	0.40
Hypoglycemia	74 (6.2%)	44 (3.7%)		0.006
Vomiting	194 (16.2)	100 (8.4%)		<0.001
Mean number of treated Infectious complications	0.21	0.22		0.72

Harvey SE, et al. *N Engl J Med.* 2014;371(18):1673-1684.

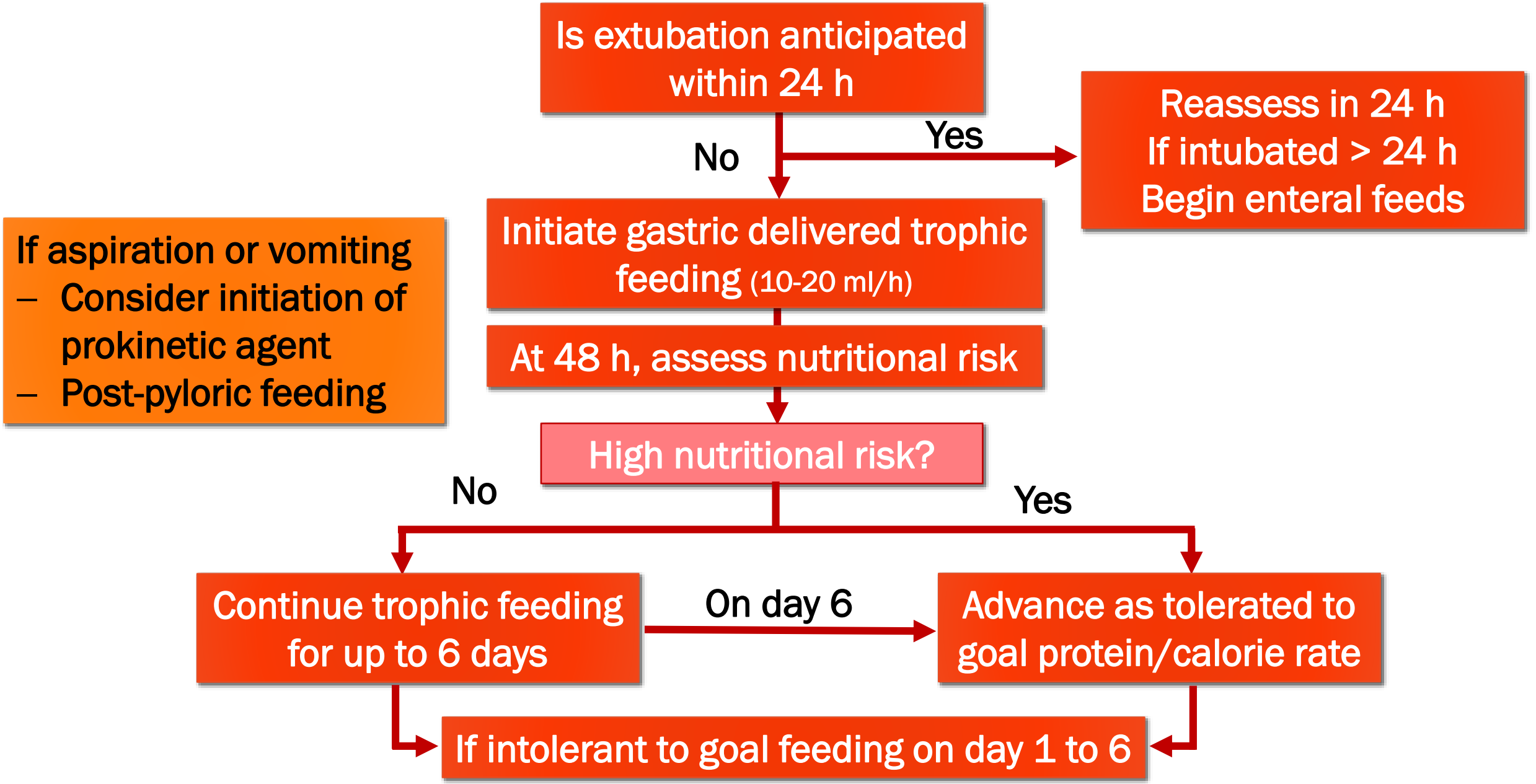


No. at Risk							
Parenteral route	1191	875	797	776	763	752	745
Enteral route	1197	844	788	766	751	736	726

Harvey SE, et al. *N Engl J Med.* 2014;371(18):1673-1684.



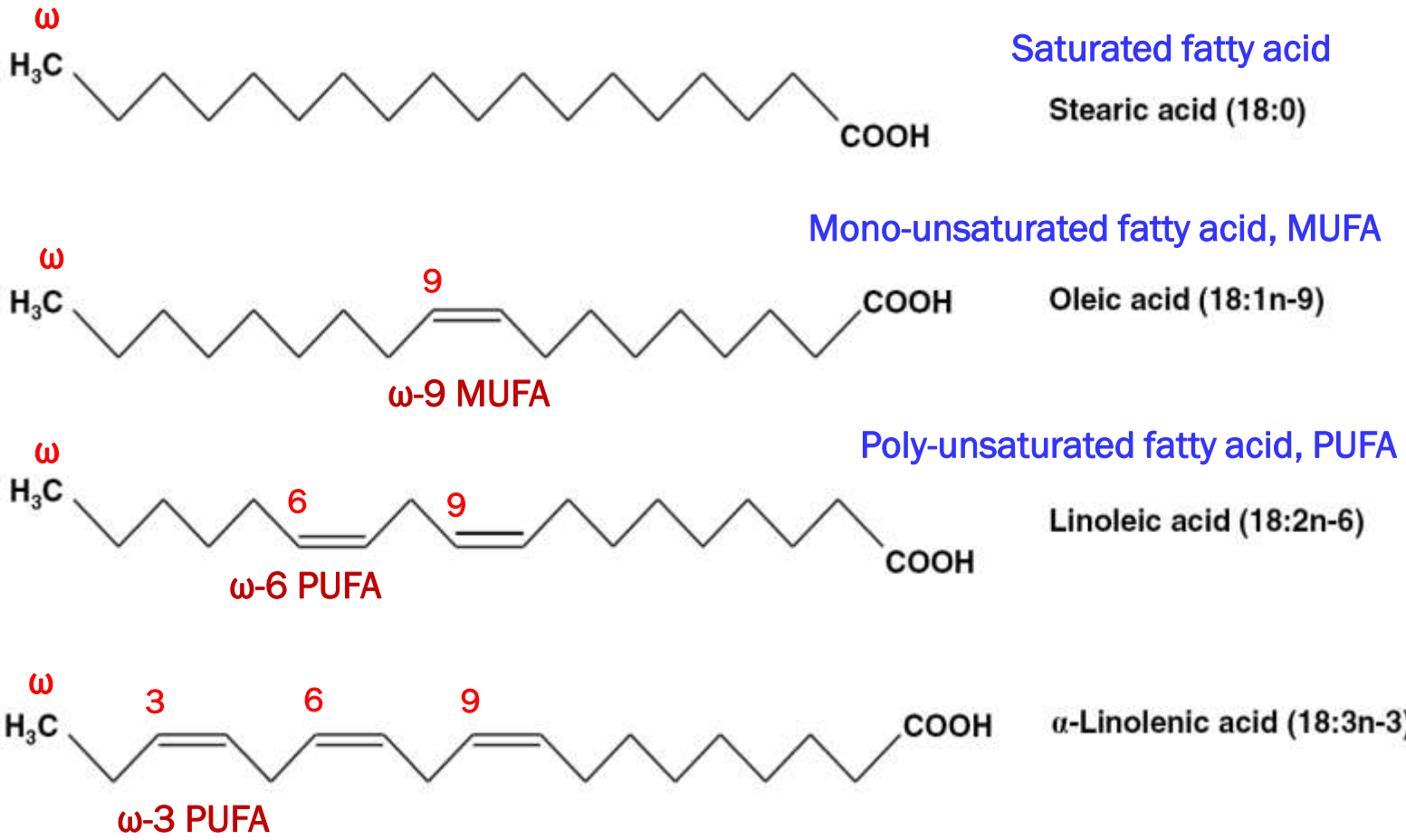
Harvey SE, et al. *N Engl J Med.* 2014;371(18):1673-1684.



Desai SV, et al. *Chest.* 2014;145(5):1148-1157.

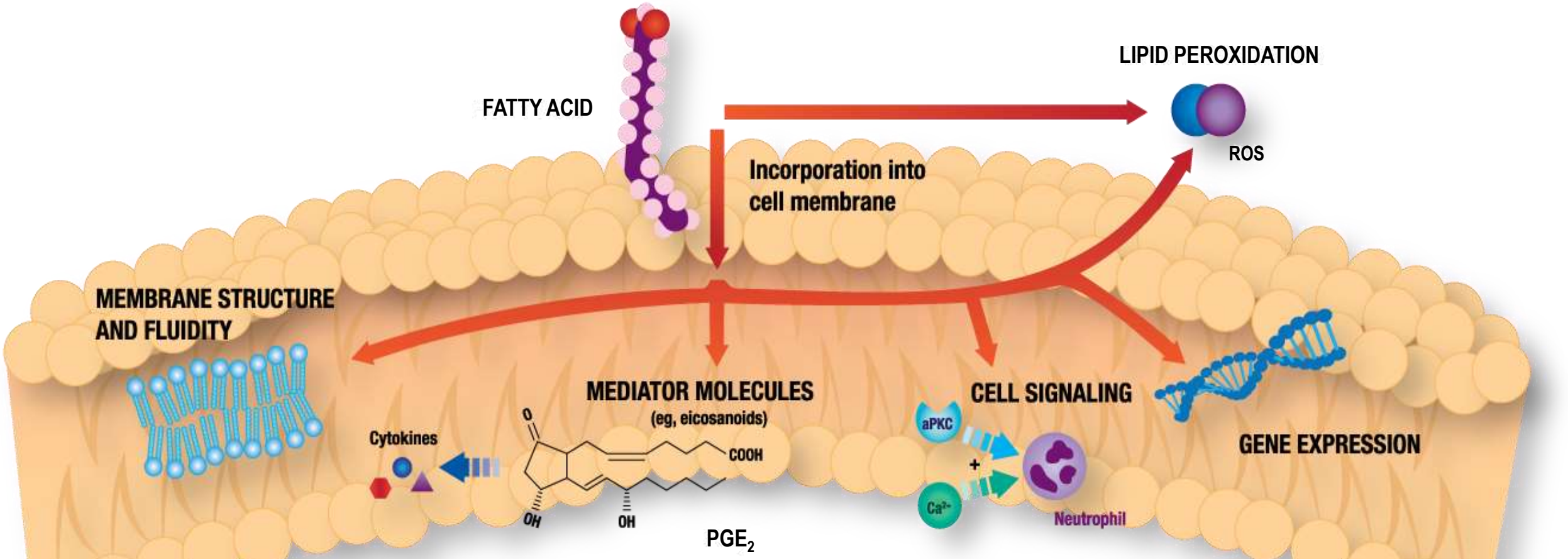
Fatty acids: structure and nomenclature

- Chain length
  - Short-chain FA: <6 Cs
  - Medium-chain FA: 6-12 Cs
  - Long-chain FA: >12 Cs
- Number and position of double bonds

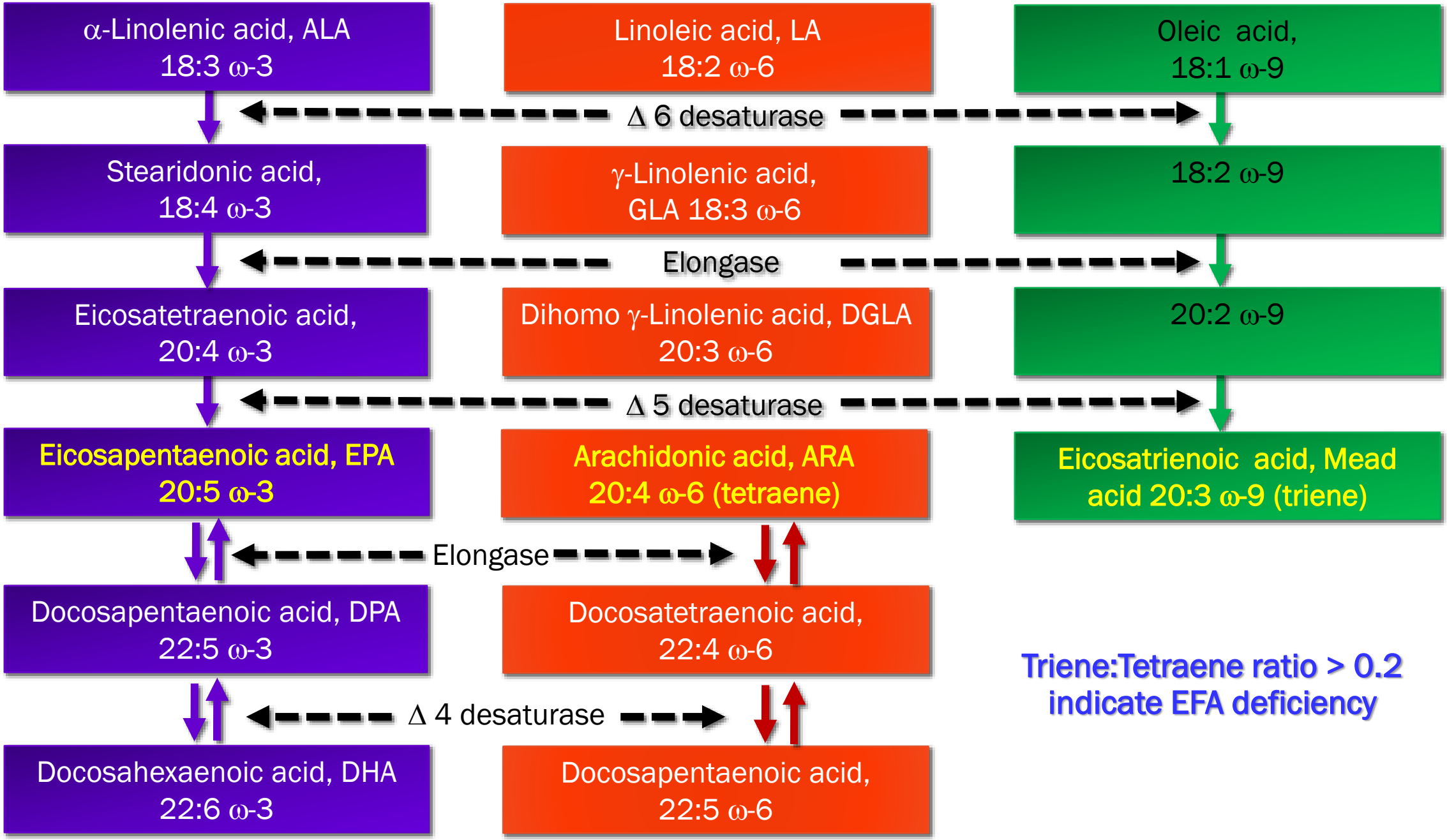


Role of fatty acids

- Fuels
  - Stored as TG in adipose tissue
  - FAs release and used for energy production in β-oxidation pathway in mitochondria (9 kcal/g)
  - SCFA, MCFA readily penetrate mitochondria (not require carnitine)
  - To prevent deficiency of essential fatty acids (EFA)
  - To avoid side effects of high amounts of glucose
  - To carry fat-soluble vitamins
- Membrane components
- Signal transduction
  - ARA-main precursor for Eicosanoids production
  - COX – yields the PGs and TXs
  - LOX – yields the LTs, HPETE, lipoxins
- Cell signaling
- Gene expression

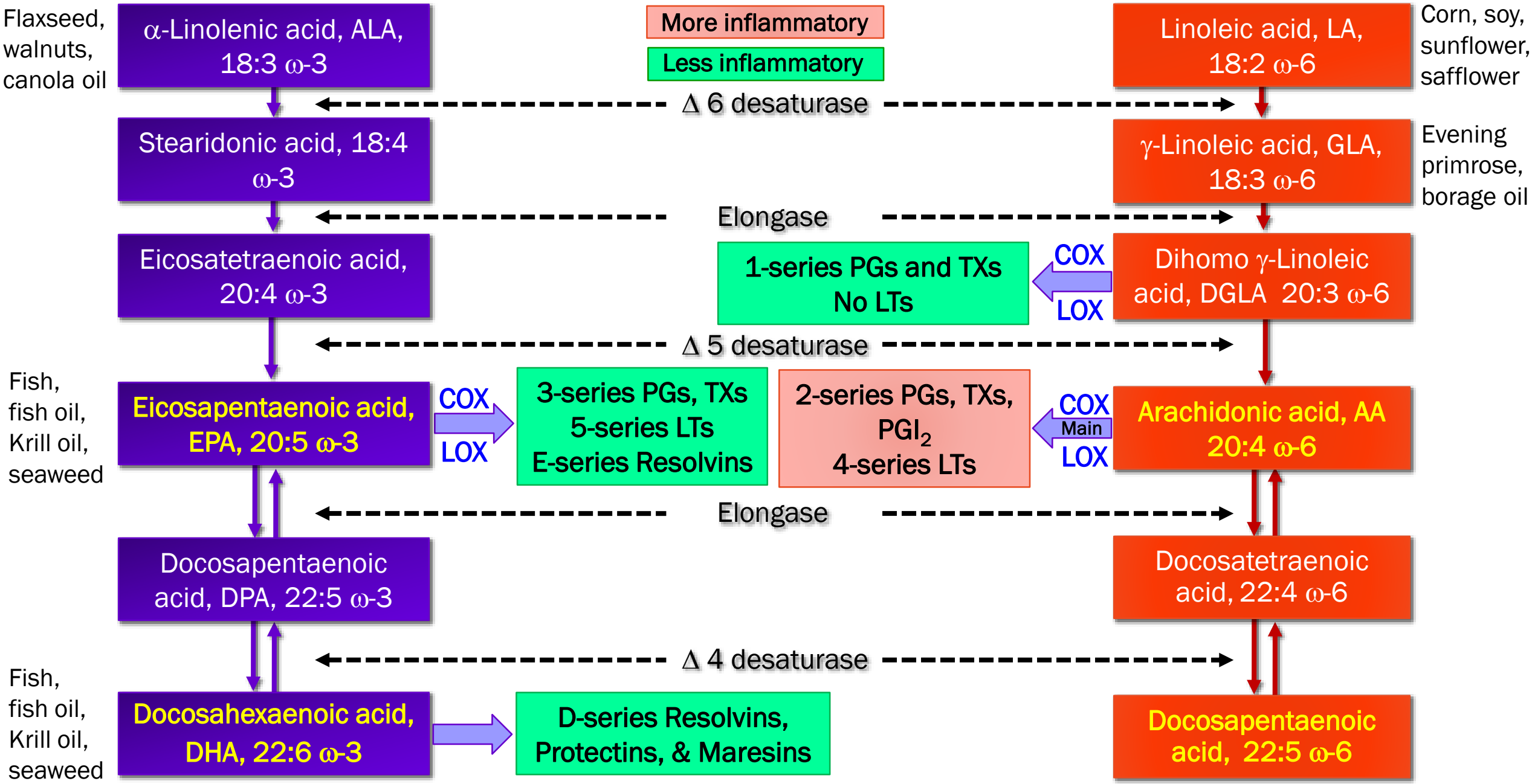


1. Contribute to cell membrane “fluidity”
2. Precursors for biological mediators (Eicosanoids and Prostaglandins)
3. Act as cell signaling molecules
4. Alter gene expression



Triene:Tetraene ratio > 0.2
indicate EFA deficiency

Biosynthesis of Fatty acids



Poudyal H, et al. Prog Lipid Res. 2011 Oct;50(4):372-87

	LCT-based (PUFA-rich)	Reduce LCT (ω-6) Introduce MCT		Introduce ω-3 and/or ω-9 (Reduce ω-6 and SFA)			
	Intralipid 20%	Lipofundin MCT-LCT 20%	Structolipid 20%	ClinOleic 20%	Lipidem 20%	SMOF lipid 20%	Omegaven 10%
Oil source	100% soy	50% coconut 50% soy	36% coconut 64% soy	80% olive 20% soy	50% coconut 40% soy 10% fish	30% soy 30% coconut 25% olive 15% fish	100% fish
SFA (%)	15.0	59.4	46.3	14.5	58.0	40.6	21.2
MUFA (%)	24.0	11.0	14.0	63.7	11.5	29.3	24.3
PUFA (%)	61.1	33.8	40.0	22.0	26.8	26.4	42.3
ω-3 (%)	8.0	4.5	5.0	2.8	5.4	7.3	35.2
ω-6 (%)	53.1	29.3	35.0	19.2	21.5	19.1	7.1
ω-9 (%)	24.0	11.0	14.0	62.3	10.6	27.7	15.1
ω-6:ω:3	7:1	7:1	7:1	9:1	2.7:1	2.5:1	1:8

Wanten GJA, Calder PC. *Am J Clin Nutr*. 2007;85(5):1171-1184.
Driscoll DF. *Nutr Clin Pract*. 2006;21(4):381-386.

IVLE: safety and toxicity

- Physicochemical stability
  - Size of LE droplets: proportion of droplet >5μm not exceed 0.05%
  - Avoid adding components that lower pH or impose ionic stress
- Hypertriglyceridemia and fat overload syndrome
  - Infusion 0.8-1.5 g/kg/d but the infusion rate not exceed 2.6/g/kg/d (0.11 g/kg/h)
  - Fat overload syndrome: headaches, fever, jaundice, abdominal pain, hepatosplenomegaly, pancytopenia and RDS
  - FO-LE accelerating lipolysis and TG clearance
  - Phospholipid interfere LPL activity (more in 10% IVLE-TG clearance slower)
- Liver dysfunction
  - Excess n-6 FA→ pro-inflammatory cytokines
  - Accumulation of hepatotoxic phytosterol

IVLE: safety and toxicity

- Pulmonary dysfunction
  - Decrease SO-LE, dose of IVLE, continuous infusion
- Oxidative stress and bioactive emulsion components other than lipid
  - OO-LE, Adding vitamin E
- Bleeding
  - high dose fish oil (up to 4 g daily) did not increase the risk of bleeding when taken with aspirin and the antiplatelet agent clopidogrel (Watson et al. 2009)
  - FO-LE did not increase risk of bleeding (Brown WV. 2011)
- Infections
  - Depends on type of FA
  - New generation of IVLE – less proinflammatory cytokine and less likely to be immunosuppression and have stronger anti-oxidant effect

Effects of a fish oil containing lipid emulsion on plasma phospholipid fatty acids, inflammatory markers, and clinical outcomes in septic patients: RCT

	Fish oil group				MCT/LCT group			
	Admission (n = 13)	Day 1 (n = 13)	Day 2 (n = 13)	Day 6 (n = 11)	Admission (n = 10)	Day 1 (n = 10)	Day 2 (n = 10)	Day 6 (n = 10)
pH	7.27 ± 0.15	7.38 ± 0.11	7.41 ± 0.12	7.42 ± 0.06	7.37 ± 0.09	7.38 ± 0.11	7.44 ± 0.06	7.43 ± 0.1
Lactate (mmol/L)	3.2 ± 1.8	4.0 ± 1.7	4.5 ± 4.8	1.9 ± 0.7	2.7 ± 1.9	3.3 ± 1.9	2.4 ± 1.2	3.1 ± 2.7
PO_2 (mm Hg)	198 ± 121	138 ± 45	127 ± 42	132 ± 44	178 ± 80	136 ± 42	145 ± 33	112 ± 38
PCO_2 (mm Hg)	78 ± 125	39 ± 7	41 ± 6	48 ± 8*	36 ± 8	39 ± 10	40 ± 8	40 ± 8
PO_2/FiO_2	269 ± 125	248 ± 81	253 ± 102	331 ± 71**	262 ± 132	252 ± 125	299 ± 80	245 ± 107
PEEP (cm H_20)	5 (5, 7)	5 (5, 7)	5 (5, 7)	5 (5, 9)	5 (5, 6)	5 (5, 7)	5 (5, 6)	5 (5, 8)

Barbosa VM. Crit Care 2010;14(1):R5

Effects of a fish oil containing lipid emulsion on plasma phospholipid fatty acids, inflammatory markers, and clinical outcomes in septic patients: RCT

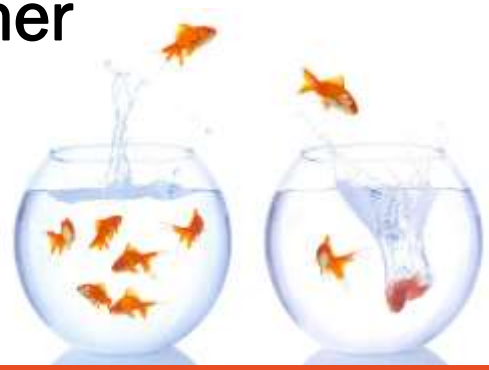
	Fish oil group (n = 13)	MCT/LCT group (n = 10)
Ventilated days	10 ± 4	11 ± 4
(excluding three patients who died in <5 days)	(11 ± 5)	(12 ± 4)
ICU stay (days)		4
(excluding three patients days)		4)
Length of hospital stay (c		16
(excluding three patients days)		17
(excluding all eight patients who died)	28 ± 9	82 ± 19
five day mortality	15% (2 out of 13)	10% (1 out of 10)
28 day mortality	31% (4 out of 13)	40% (4 out of 10)

IVLE containing FO in septic ICU patients increases plasma EPA, modified inflammatory cytokines concentrations and improves gas exchange. These changes are associated with a tendency toward shorter LOS (p=0.079)

Barbosa VM. Crit Care 2010;14(1):R5

Supplement n-3 FA in critically ill

- 8 studies (n=391), overall trial quality—poor
- *A significant reduction in hospital length of stay of 9.49 days (95% CI–16.51, –2.47; p = 0.008) was observed for those receiving ω-3 FA supplemented PN, but results were strongly influenced by one small study*
- Although ω-3 FA appear to reduce hospital length of stay, the poor methodology of the included studies and the absence of other outcome improvements mean they cannot be presently recommended.



Palmer AJ, et al. *Crit Care Med. 2013;41(1):307-316.*

Pradelli *et al. Critical Care* 2012, **16**:R184
http://ccforum.com/content/16/5/R184

CRITICAL CARE

RESEARCH Open Access

n-3 fatty acid-enriched parenteral nutrition regimens in elective surgical and ICU patients: a meta-analysis

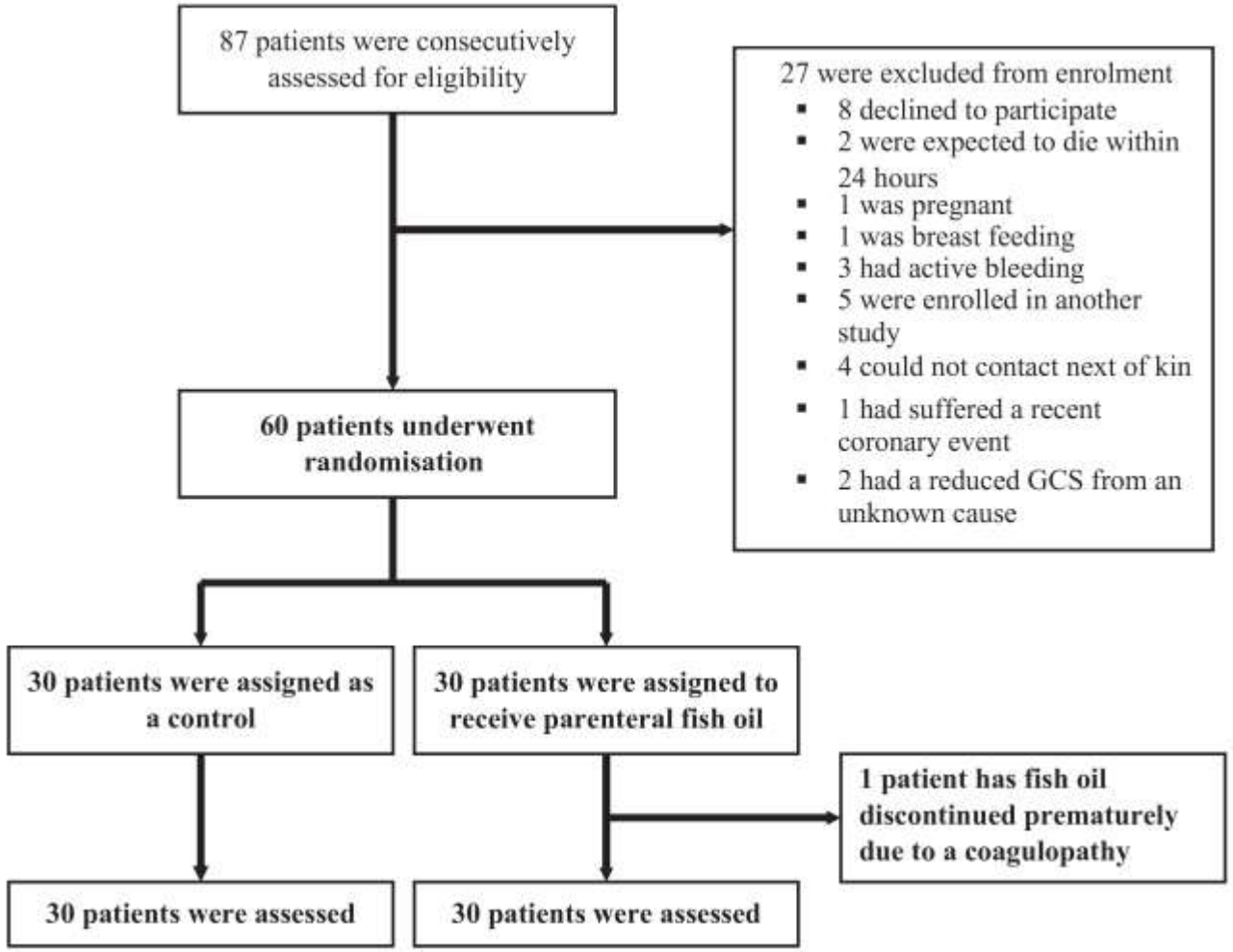
Lorenzo Pradelli[1*], Konstantin Mayer[2], Maurizio Muscaritoli[3]

Results: A total of 23 studies (n = 1502 patients: n = 762 admitted to the ICU) were included. No statistically significant difference in mortality rate was found between patients receiving n-3 PUFA-enriched lipid emulsions and those receiving standard lipid emulsions (RR= 0.89; 0.59, 1.33), possibly reflecting a relatively low underlying mortality risk. However, n-3 PUFA-enriched emulsions are associated with a statistically and clinically significant reduction in the infection rate (RR =0.61; 0.45, 0.84) and the lengths of stay, both in the ICU (-1.92; -3.27, -0.58) and in hospital overall (-3.29; -5.13, -1.45). Other beneficial effects included reduced markers of inflammation, improved lung gas exchange, liver function, antioxidant status and fatty acid composition of plasma phospholipids, and a trend towards less impairment of kidney function.

Conclusions: These results confirm and extend previous findings, indicating that n-3 PUFAs-enriched parenteral nutrition regimens are safe and effective in reducing the infection rate and hospital/ICU stay in surgical and ICU patients.

Pradelli L, et al. *Crit Care. Oct 4, 2012;16(5):R184.*

Parenteral Fish Oil on Survival Outcomes in Critically Ill Patients With Sepsis

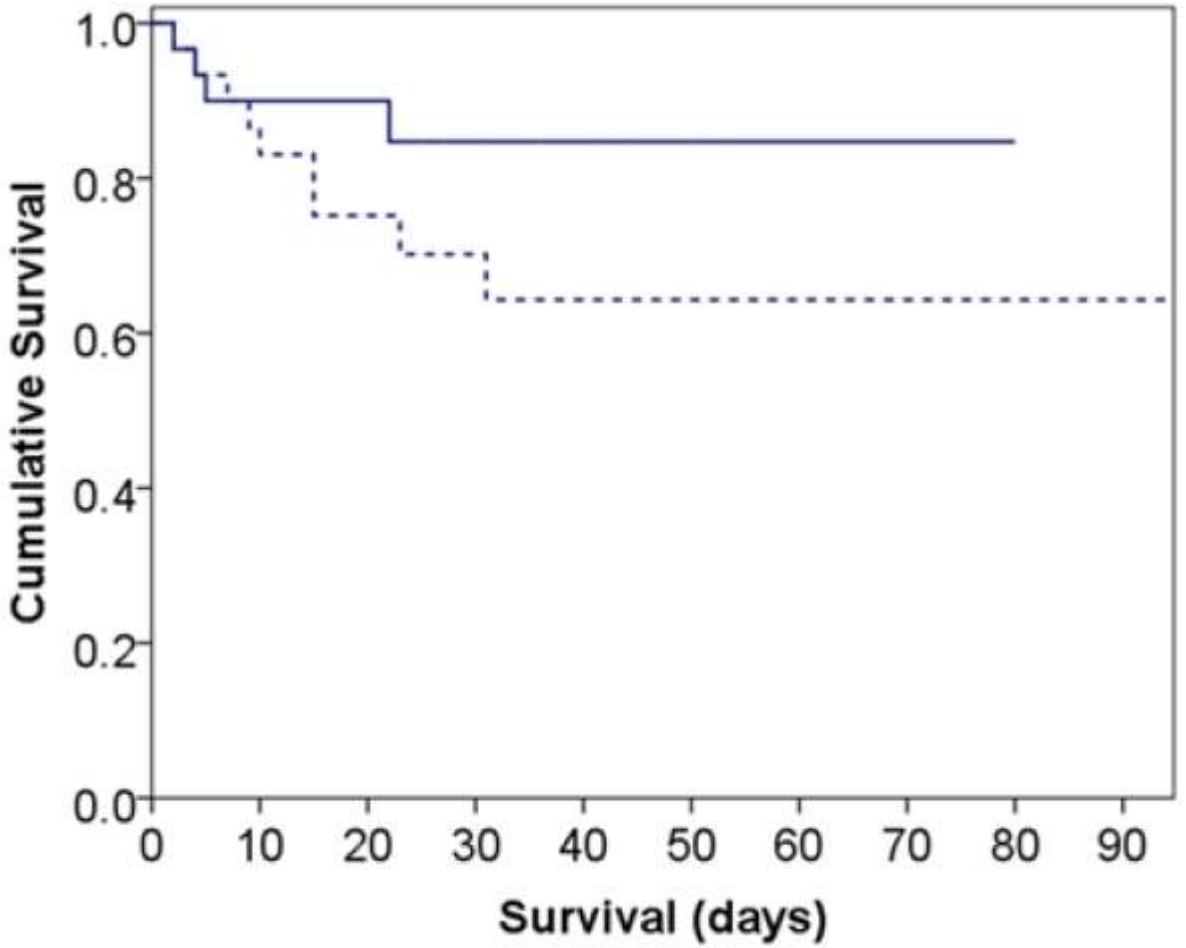


- Septic patients were enrolled into the study within 12 hrs of ICU admission or within 12 hrs of new-onset sepsis (n=60)
- Standard care vs. standard care +FO (Omegaven 0.2 g FO/kg/d) daily for 14 d (or discharge)

Hall TC, et al. *JPEN* 2015 Mar;39(3):301-12 (Epub:2014 Jan 9).

Parenteral Fish Oil on Survival Outcomes in Critically Ill Patients With Sepsis

- Parenteral ω-3 were associated with a significant reduction in new organ dysfunction and CRP
- Patients with less severe sepsis (n = 35; predicted mortality of ≤ 40% based on the admission APACHE II score) treated with ω-3 had a significant reduction in mortality (*P = 0.042).*

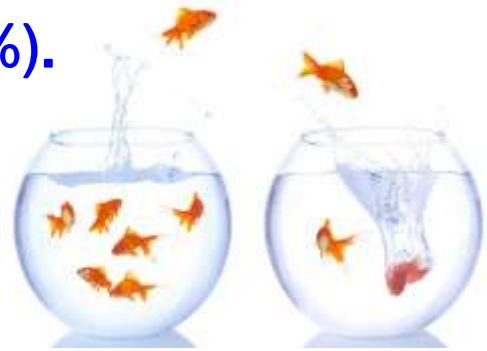


Hall TC, et al. *JPEN* 2015 Mar;39(3):301-12 (Epub:2014 Jan 9).

FO IVLE in critically ill patients

- 6 RCTs (n = 390) most trials use FO IVLE 0.1 -0.2 g/kg/d
- FO-containing emulsions were associated with
  - A trend toward a reduction in mortality (RR=0.71: 0.49–1.04; P = .08)
  - A trend toward a reduction in the duration of MV (WMD=−1.41 d: −3.43 to 0.61; P = .17)
  - No effect on infections (RR= 0.76: 0.42–1.36; P = 0.35) and ICU LOS (WMD= −0.46: −4.87 to 3.95; P = 0.84, heterogeneity I2 = 75%).

There is inadequate evidence to recommend the routine use of parenteral FO



Manzanares W, et al. *JPEN* 2014;38(1):20-28.

Lipids in PN: what do the guidelines say?

Guideline	Key points
ASPEN position paper on alternative lipid emulsions	• MCTs, olive oils and fish oils have an equivalent safety profile to soybean oil • These alternative IVLEs are metabolised via different pathways, which may lead to less pro-inflammatory effects and less immune suppression • Many patients who require IVLE are already in a compromised state and may benefit from receiving an alternative IVLE to diminish the intake of the potentially pro-inflammatory ω-6 linoleic acid (>50% of the fatty acid profile in soybean oil)
SCCM/ASPEN guidelines in ICU patients	• In the first week of hospitalization in the ICU, when PN is required and EN is not feasible, patients should be given a parenteral formulation without soy-based lipids
Canadian critical care nutrition guidelines	• When PN with IVLEs is indicated, lipids that reduce the load of ω-6 FAs should be considered • There are insufficient data to make a recommendation on the type of lipids to be used that reduce the ω-6 FA/soybean oil load in critically ill patients receiving PN

Lipids in PN: what do the guidelines say?

Guideline	Key points
ESPEN guidelines in ICU patients	• Lipids should be an integral part of PN for energy and to ensure EFA provision • IVLE can be administered safely at a rate of 0.7–1.5g/kg over 12–24 hours • The tolerance of mixed LCT / MCT IVLEs is sufficiently documented • Olive oil-based PN is well-tolerated in critically ill patients
ESPEN guidelines in non-surgical oncology patients	• Using a higher than usual percentage of lipid (e.g. 50% of non-protein energy) may be beneficial for those with frank cachexia needing prolonged PN
ASPEN guidelines in paediatric patients[3]	• IVLE should be given in a sufficient dose to avoid EFA deficiency • In very low birthweight infants, the use of 20% IVLE requires accurate and low flow pump delivery systems • In general, 3 g/kg/day is the accepted limit for IVLE administration in small-for -gestational-age neonates and preterm neonates

Summary

- Nutrition assessment and calculate of nutrient requirements to determine goal of nutritional therapy
- Initiate enteral nutrition (EN) within 24–48 hr following the onset of critical illness and admission to the ICU, and increase to goals over the first week of ICU stay.
- Take steps as needed to reduce risk of aspiration or improve tolerance to gastric feeding (use prokinetic agent, continuous infusion, chlorhexidine mouthwash, elevate the head of bed, and divert level of feeding in the gastrointestinal tract).
- Implement enteral feeding protocols with institution-specific strategies to promote delivery of EN.
- Do not use gastric residual volumes as part of routine care to monitor ICU patients receiving EN.
- Start parenteral nutrition early when EN is not feasible or sufficient in high-risk or poorly nourished patients.