Critical Care Nutrition Research: Part 1

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Energy intake?
Trophic versus full feeding

20 minutes in groups
20 minutes group presentations

What is wrong with this paper?

Study the papers and give arguments

SPN-trial

Heidegger C. et al. Lancet 2013; 381: 385–93

1. What were the primary and secondary endpoints? And how were they defined?
2. What is a univariate versus multivariate analysis with respect to the primary endpoint? Why are the significant results different in univariate versus multivariate analysis?
3. Are the conclusions with respect to reductions in infections based on the presented research acceptable?

PERMIT-trial

Arabi Y. New Engl J Med, May 20, 2015,

4. What does the Kaplan Meier Survival Curve show, and what does it mean? What if baseline variables are not balanced (significant differences among groups)
5. What are differences between prespecified and non-prespecified subgroup analyses (e.g. medical versus surgical, below 65 years or over, males versus females, diabetes versus non-diabetes
6. Should this trial lead to recommendations favouring trophic feeding over full feeding to all ICU patients? external validity

What to do?

Group 1
What were the primary and secondary endpoints? And how were they defined?

SPN trial: primary end point

- **Primary end point:**

  occurrence of nosocomial infections after day **8 until day 28**. Infections were defined according to definitions from the Centers for Disease Control and Prevention.

- **Five infection categories:**

  1. **pneumonia** (ventilator or nonventilator-associated pneumonia, and other lower respiratory tract infections);
  2. **bloodstream infection** (laboratory-confirmed bloodstream infections and clinical sepsis);
  3. **urogenital infection** (device-associated or non-device-associated urinary tract and genital infections);
  4. **abdominal infection** (intra-abdominal infections);
  5. **and other infection** (skin, bone, and soft tissue infections; ear, nose, and throat infections; upper respiratory and intrathoracic infections).

Heidegger CP. Lancet 2013; 381: 385–93

SPN trial: secondary end points

- **Secondary end points:**
  1. Number of antibiotic days (defined as days from day 1 to day 28 during which a patient received at least one dose of antibiotics) for nosocomial infection and number of antibiotic-free days (days during which a patient did not receive antibiotics; if a patient died, antibiotic-free days were censored at death). Antibiotics were given to treat infection and as a prophylaxis.
  2. Duration of invasive and non-invasive mechanical ventilation
  3. Length of stay in the ICU and hospital until day 28
  4. Mortality in the ICU,
  5. General mortality (hospital)
  6. Duration of renal replacement therapy,
  7. Glycaemia (crude blood glucose concentration and area under the curve [AUC]),
  8. Phosphataemia,
  9. Concentration of C-reactive protein,
  10. Liver test results, and
  11. Drug administration (insulin, steroids, and anti fungal agents).

Heidegger CP. Lancet 2013; 381: 385–93

SPN trial: primary end point

- **Primary end point:**

  Power calculation:

  - An assumed overall infection rate of 50% in the targeted patient population, on the basis of results from our previous study,[11] which showed an incidence of 57% of nosocomial infections in patients admitted to the ICU for more than 5 days.
  - Postulated that full coverage of energy needs might decrease the infection rate by 33%.
  - To detect such an effect with a statistical power level of 80%, 148 patients had to be included in each group.

- **Secondary end points:**

  Hypothesis generating, not powered

Heidegger CP. Lancet 2013; 381: 385–93

Group 2
What is a univariate versus multivariate analysis with respect to the primary endpoint?
Why are the significant results different in univariate versus multivariate analysis?

Heidegger CP. Lancet 2013; 381: 385–93

SPN trial:
univariate vs. multivariate analysis

- **Primary end point:**

  occurrence of nosocomial infections after day **8 until day 28.** Infections were defined according to definitions from the Centers for Disease Control and Prevention.

- **Univariate:**

  all variables (on baseline) that have an effect on the primary outcome.

- **Multivariate:**

  the combined effect of selected variables on the primary outcome

Heidegger CP. Lancet 2013; 381: 385–93

SPN trial: univariate vs. multivariate analysis

P < 0.05 significant
P < 0.10 trend

	Univariable analysis		Multivariable analysis*	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Sex (women vs men)	1·02 (0·66–1·58)	0·9265	..	..
Age (1-year increase)	0·99 (0·98–1·00)	0·1934	..	..
SAPS II score (1-point increase)	1·01 (1·00–1·03)	0·0491	..	..
Body-mass index (1-kg/m² increase)	1·04 (0·99–1·08)	0·1205	..	..
Hospital (Geneva vs Lausanne)	1·18 (0·78–1·78)	0·4377	..	..
Study intervention (SPN vs EN)	0·62 (0·42–0·93)	0·0200	0·65 (0·43–0·97)	0·0338÷
Admission category (surgery vs medicine)	1·01 (0·68–1·50)	0·9488	..	..
Antibiotics before day 9 (yes vs no)	1·20 (0·70–2·05)	0·5048	..	..
Infections before day 9 (yes vs no)	0·84 (0·56–1·26)	0·3958	..	..
Mechanical ventilation before day 9 (yes vs no)	1·53 (0·94–2·50)	0·0897	..	..

Univariable and multivariable Cox regression model. SAPS II=Simplified Acute Physiology II score. SPN=supplemental parenteral nutrition. EN=enteral nutrition. *Variables in the multivariable analysis were SAPS II score, hospital, study intervention, admission category, previous antibiotic use before day 9, and mechanical ventilation before day 9. ÷Statistically significant with Benjamini-Hochberg correction.

***Table 2:* Univariable and multivariable Cox regression model for first nosocomial infection during follow-up (primary endpoint)**

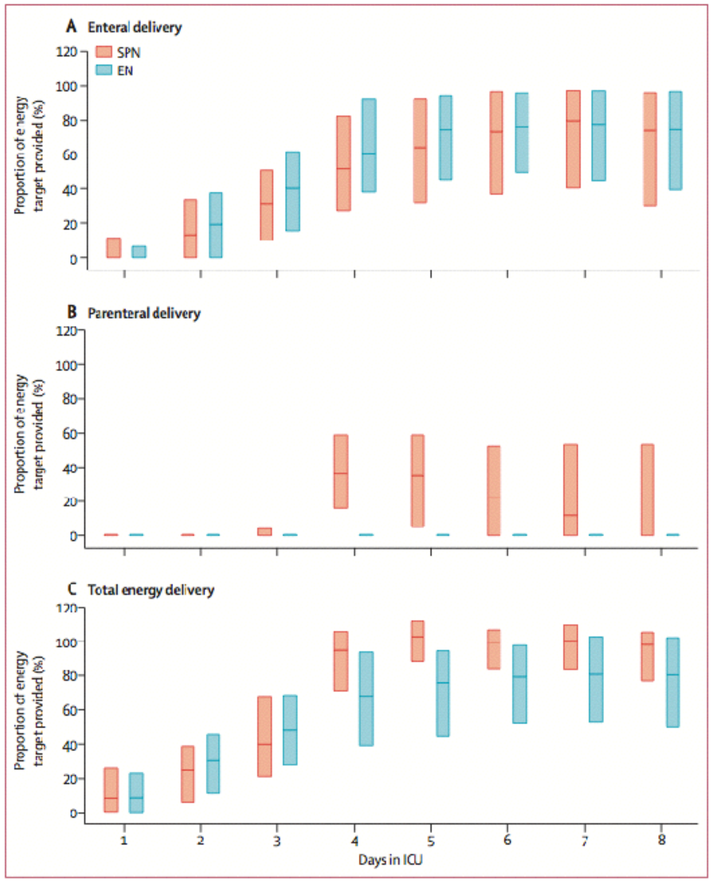
Heidegger CP. Lancet 2013; 381: 385–93

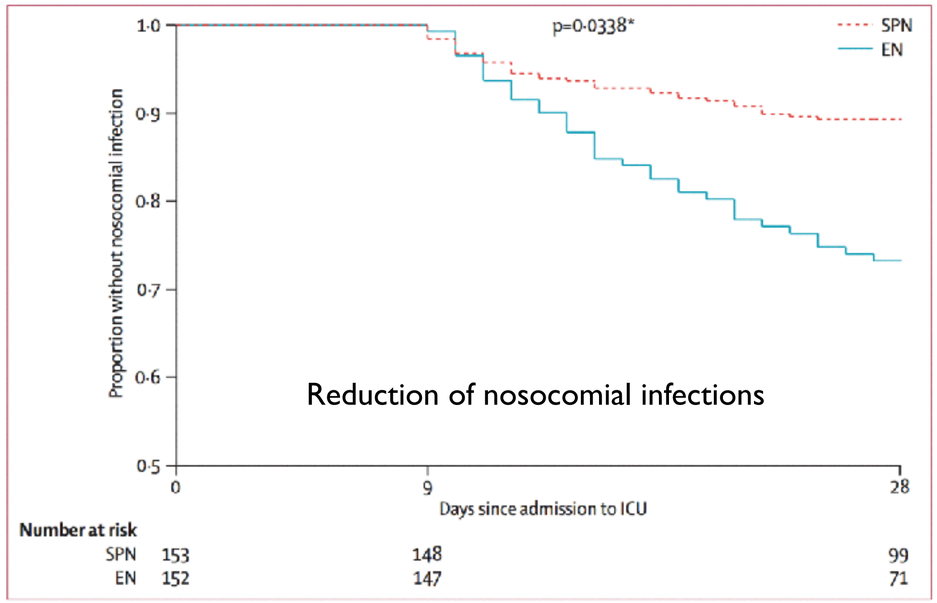
Group 3
Are the conclusions with respect to reductions in infections based on the presented research acceptable?

Heidegger CP. Lancet 2013; 381: 385–93

Supplemental Parenteral Nutrition (SPN) Trial

153 patients SPN (unable to tolerate 60% EN target on day 3) and 152 EN





En delivery day 4-8: 28 kcal/kg*day in SPN group (103% of target), compared with 20 kcal/kg* in EN group (77%)

Heidegger CP. Lancet 2013; 381: 385–93

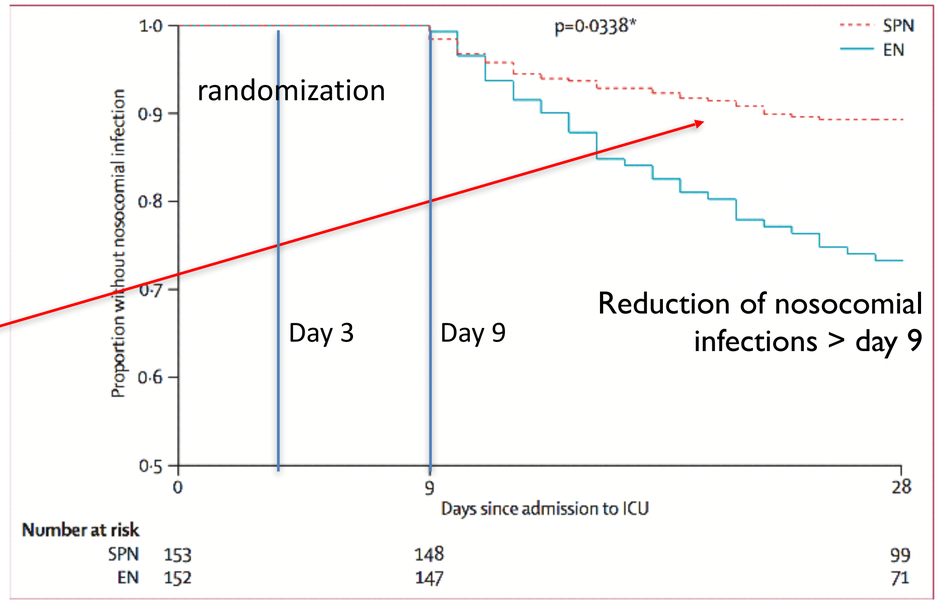
Supplemental Parenteral Nutrition (SPN) Trial

153 patients SPN (unable to tolerate 60% EN target on day 3) and 152 EN

	Enteral nutrition	Supplemental parenteral nutrition
Day 4–8	18%	23%
Day 9–28	21%	15%
Day 4–28	39%	37%*

Data are % of patients. Data obtained from reference 1. *Difference not statistically significant.

Table: Rate of hospital acquired pneumonia



New infections after randomization on day 3
SPN has no Effect on Infections!

Heidegger CP. Lancet 2013; 381: 385–93

Group 4
What does the Kaplan Meier Survival Curve show, and what does it mean? What if baseline variables are not balanced (significant differences among groups)?

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Weisenthal Cancer Group

Kaplan-meier curve

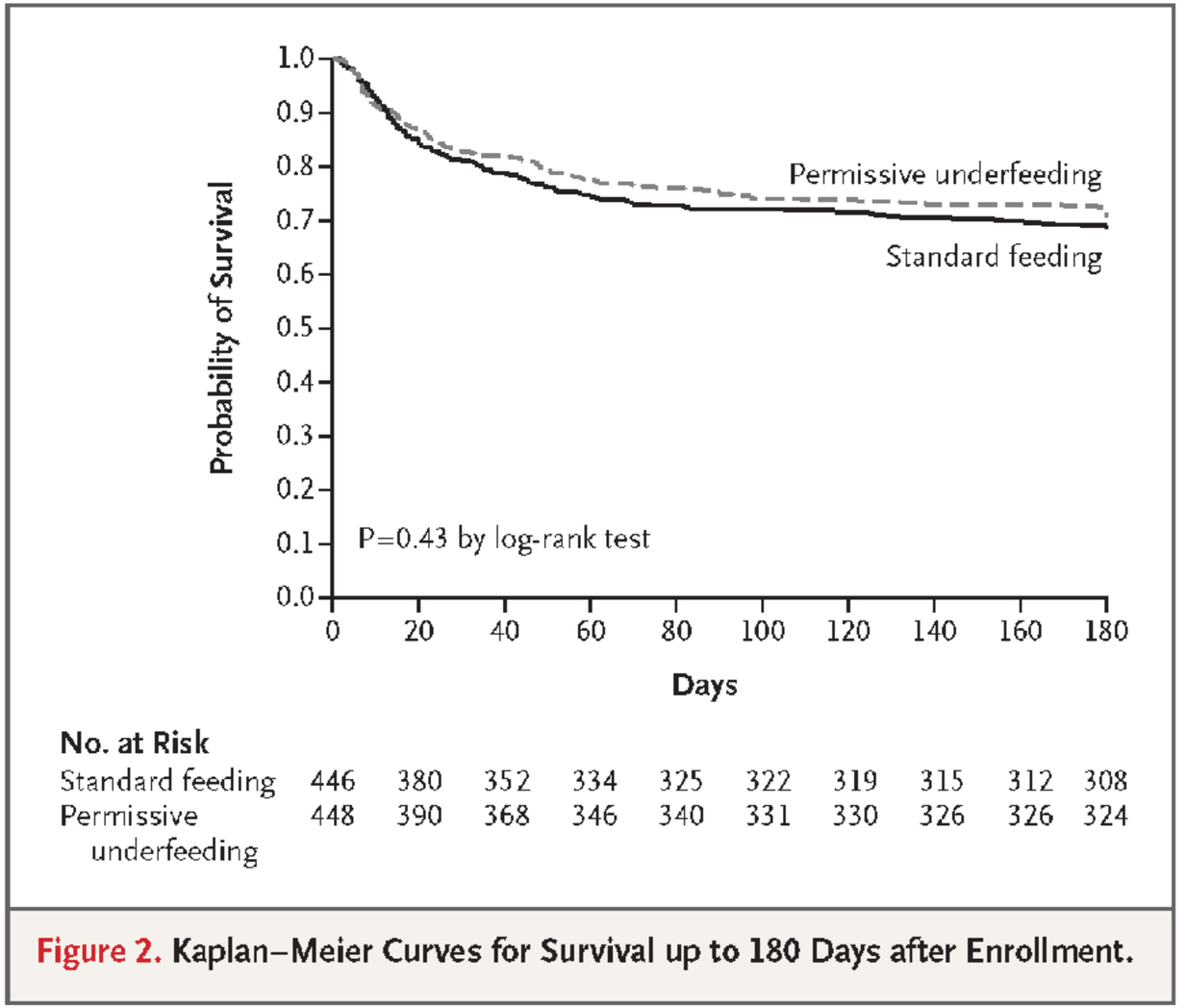

Figure 2. Kaplan–Meier Curves for Survival up to 180 Days after Enrollment.

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Kaplan-meier curve

KM-analysis = Univariate

- 2 groups only outcome mortality
- log-rank test
- no correction for baseline risk

- Check table 1:
- No differences in baseline

Table 1. Baseline Characteristics of the Patients, According to Study Group.*

Variable	Permissive Underfeeding (N=448)	Standard Feeding (N=446)
Age — yr	50.2–9.5	50.9–19.4
Female sex — no. (%)	256 (54.8)	264 (56.8)
Body-mass index†	29.0–8.2	29.7±8.8
Diabetes — no. (%)	259 (55.5)	253 (54.3)
Admission category — no. (%)		
Medical	336 (75.0)	335 (75.1)
Surgical	79 (17.7)	77 (17.3)
Nonoperative trauma	93 (20.8)	99 (22.2)
Severe sepsis at admission — no. (%)	159 (35.5)	133 (29.8)
Traumatic brain injury — no. (%)	55 (12.3)	63 (14.1)
APACHE II score‡	21.0±7.9	21.0±8.2
SOFA score§	9.0–3.5	9.8–3.5
Mechanical ventilation — no. (%)	436 (97.3)	429 (96.2)
Vasopressor therapy — no. (%)	255 (56.9)	243 (54.5)
Glycated hemoglobin — mmol/liter	0.07–0.06	0.07–0.08
C-reactive protein — mg/liter	151–80	175±82
Serum lipid levels — mmol/liter		
Triglycerides	1.56–1.07	1.58–1.17
Total cholesterol	2.66–1.07	2.77–0.98
Low-density lipoprotein	1.29±0.78	1.34±0.72
High-density lipoprotein	0.59–0.33	0.64–0.40
Albumin — g/liter	28–7	28±6
Prealbumin — g/liter	0.15±0.13	0.14±0.12
Transferrin — g/liter	1.36–0.49	1.38–0.50
24-hour urinary nitrogen excretion — mmol	284–126	309–219
Time from eligibility to randomization — hr	8.3±11.6	7.9±12.3

* Plus–minus values are means ±SD. There were no significant between-group differences. Data on laboratory values were not available for some patients; the numbers of patients with available data in the permissive underfeeding group and the standard feeding group, respectively, were as follows: glycated hemoglobin, 268 patients and 284 patients; C-reactive protein, 357 patients and 360 patients; triglycerides, 375 patients and 376 patients; total cholesterol, 373 patients and 372 patients; low-density lipoprotein, 365 patients and 363 patients; high-density lipoprotein, 374 patients and 375 patients; prealbumin, 337 patients and 341 patients; transferrin, 349 patients and 346 patients; and 24-hour urinary nitrogen excretion, 305 patients and 292 patients.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating more severe disease.

§ Scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with higher scores indicating a greater degree of organ failure.

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Group 5
What are differences between prespecified and non-prespecified subgroup analyses (e.g. medical versus surgical, below 65 years or over, males versus females, diabetes versus non-diabetes?

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(prespecified) subgroup analysis

The primary outcome was compared between the two study groups in the following prespecified subgroups:

- **nonsurgical patients versus surgical patients,**
- **patients with diabetes versus patients without diabetes,**
- **patients with an APACHE II score of <18 versus those with a score >18**
- **patients with a specific admission diagnosis (severe sepsis or traumatic brain injury) versus patients without either of those diagnoses,**
- **patients using vasopressors at baseline versus those not using them,**
- **and patients with a blood glucose level of no more than the median value at randomization versus those with a level higher than the median value.**

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(prespecified) subgroup analysis

When multiple subgroup analyses are performed, the probability of a false positive finding can be substantial.

For example, if the null hypothesis is true for each of 10 independent tests for interaction at the 0.05 significance level, the chance of at least one false positive result exceeds 40%.

Be cautious in case of non-prespecified subgroups:

Check study protocol on trial website

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Group 6
Should this trial lead to recommendations favouring trophic feeding over full feeding to all ICU patients? External validity?

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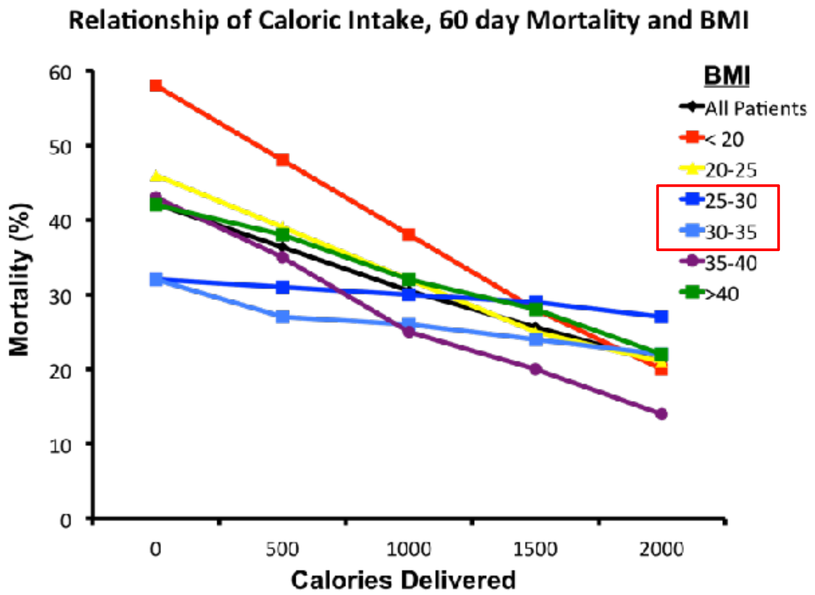
Effect of daily increase of 1000 kcal or 30 g proteins & 60 d mortality risk

BMI group	Adj. Odds Ratio	95%CI LCL	95% CI UCL	P-value
Energy	**+ 1000 kcal/day**			
overall	0.76	0.61	0.95	0.014
<20	0.52	0.29	0.95	0.033
20 to <25	0.62	0.44	0.88	0.007
25 to <30	1.05	0.75	1.49	0.768
30 to < 35	1.04	0.64	1.68	0.889
35 to < 40	0.36	0.16	0.80	0.012
≥ 40	0.63	0.32	1.24	0.180
N=2729/2728				
Proteins	**+ 30 g proteins/day**			
overall	0.84	0.74	0.96	0.008
<20	0.60	0.41	0.87	0.007
20 to <25	0.81	0.66	0.99	0.036
25 to <30	0.97	0.79	1.19	0.758
30 to < 35	1.04	0.79	1.37	0.774
35 to < 40	0.62	0.39	0.98	0.039
≥ 40	0.72	0.51	1.03	0.072



Effect if BMI <25 or >35

C Alberda Intensive Care Med. 2009;35(10):1728-37

Young patients, high BMI, severely ill ICU patients

Variable	Permissive Underfeeding (N=448)	Standard Feeding (N=446)
Age — yr	50.2±19.5	50.9±19.4
Female sex — no. (%)	156 (34.8)	164 (36.8)
Body-mass index†	29.0±8.2	29.7±8.8
Diabetes — no. (%)	159 (35.5)	153 (34.3)
Admission category — no. (%)		
Medical	336 (75.0)	335 (75.1)
Surgical	19 (4.2)	12 (2.7)
Nonoperative trauma	93 (20.8)	99 (22.2)
Severe sepsis at admission — no. (%)	159 (35.5)	133 (29.8)
Traumatic brain injury — no. (%)	55 (12.3)	63 (14.1)
APACHE II score‡	21.0±7.9	21.0±8.2
SOFA score§	9.9±3.5	9.8±3.5
Mechanical ventilation — no. (%)	436 (97.3)	429 (96.2)

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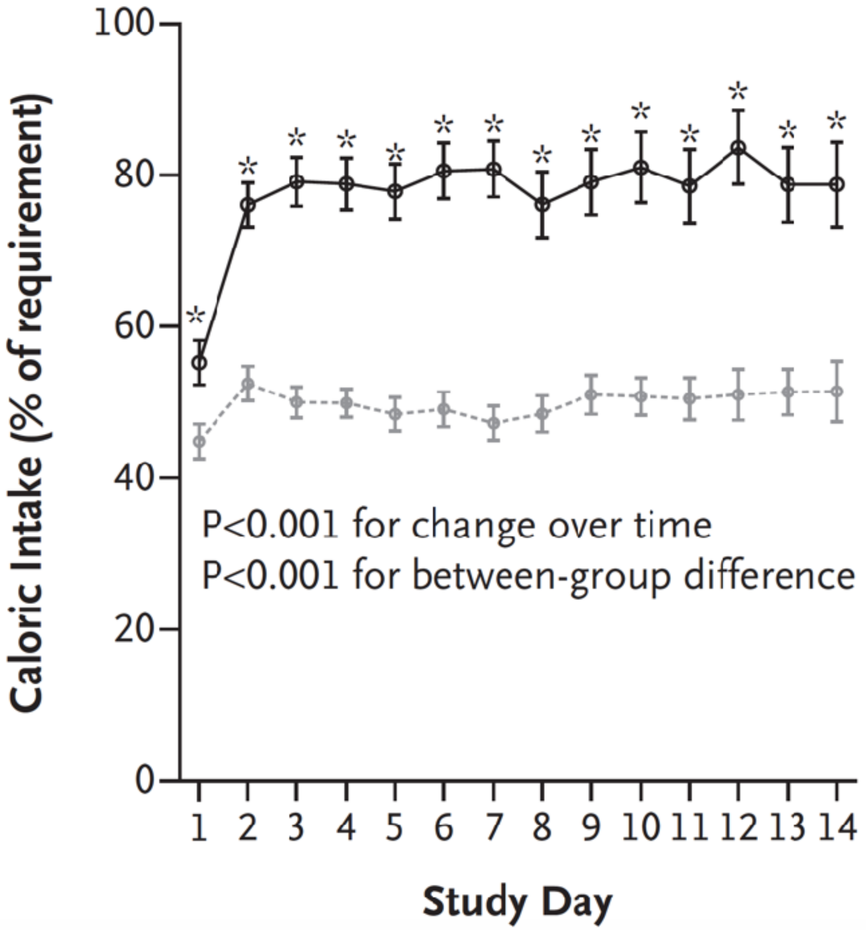
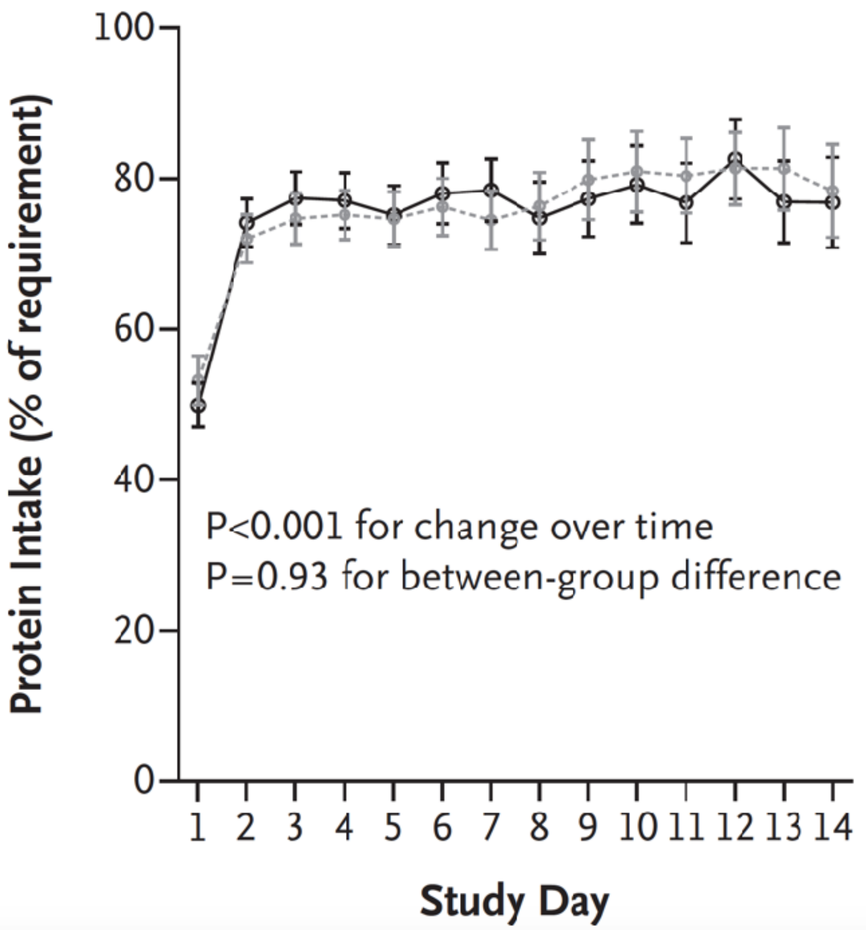
Caloric and Protein Intake





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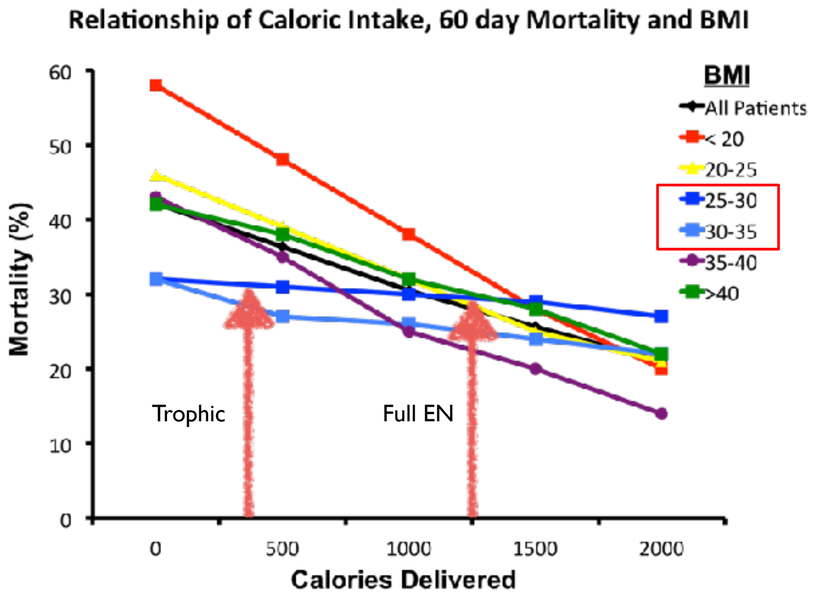
Trophic vs. Full EN in ICU patients
The ARABI randomized trial

- Average age 50
- Average BMI 29-30
- All fed within 24 hrs (benefits of early EN)



No effect of hypocaloric feeding in young, overweight patients when protein intake is compensated!

Arabi et al. New Engl J Med 2015 20 May online first

(prespecified) subgroup analysis

The trial was “pseudomulticentric” — almost 70% of the patients were recruited from one site.
No indirect calorimetry was performed.
The mean caloric intake was **low in the underfeeding and full-feeding groups (11 kcal vs. 16 kcal per kilogram of body weight per day); both intakes met the criteria for underfeeding.**
Moreover, the mean protein intake achieved (0.7 g per kilogram per day in both groups) was far below the recommended intake of 1.2 to 2.0 g per kilogram per day.
As in the Trophic vs. Full- Energy Enteral Nutrition in Mechanically Ventilated Patients with Acute Lung Injury trial,no significant differences were observed between the two groups, since the admission category of most patients was “medical” and the patients were young (mean age, 51 years) and well-nourished (mean body-mass index [the weight in kilograms divided by the square of the height in meters], 29.
Heyland and coworkers suggested that increasing caloric and protein intake is associated with improved clinical outcomes among patients with higher-nutritional-risk profiles.
Therefore, extrapolation of the permissive underfeeding concept to high-risk patients cannot be recommended.
Furthermore, long-term functional outcomes were not investigated, although they have been shown to be associated with feeding adequacy.

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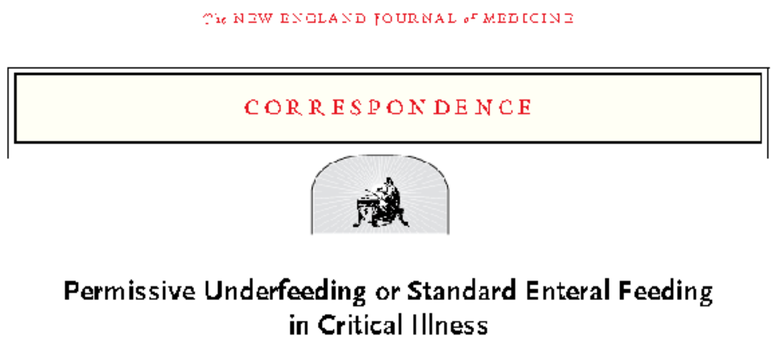

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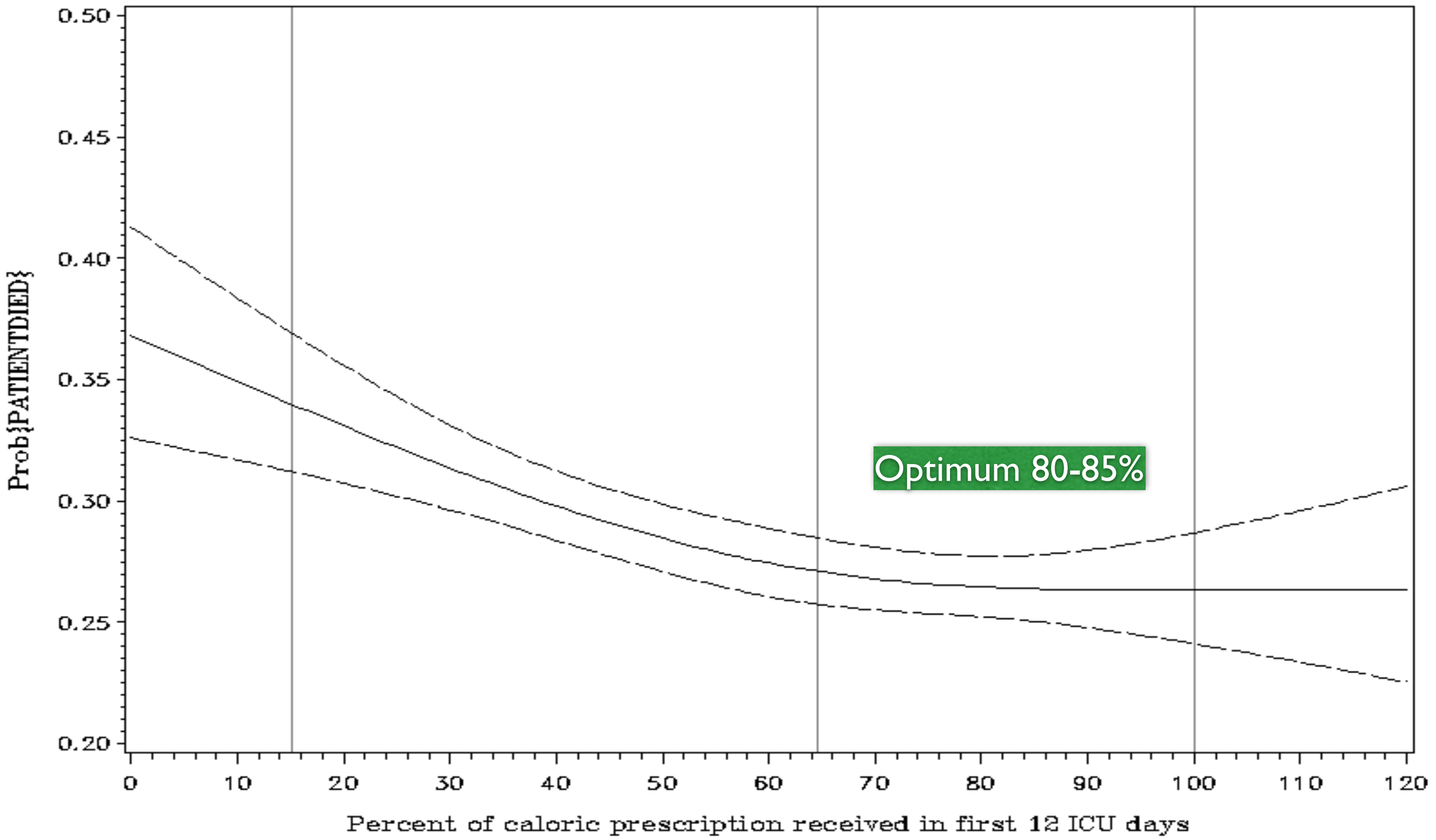
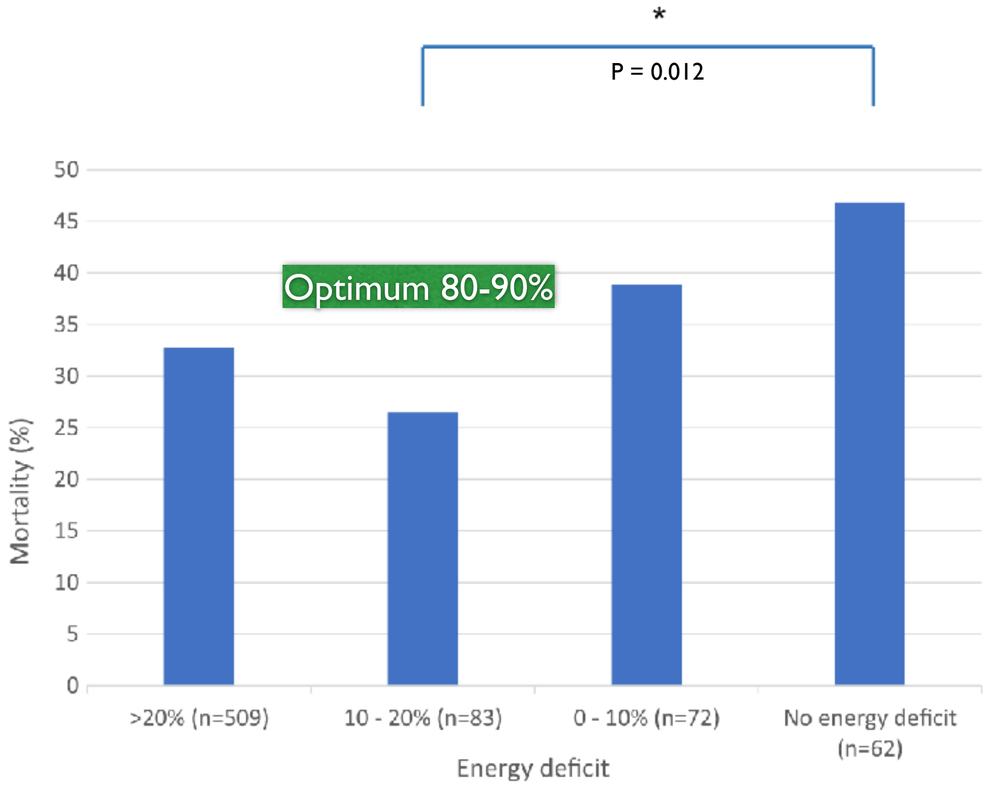
12-day Caloric Adequacy & 60-Day Hospital Mortality



Heyland D et al. Crit Care Med 2011

Hospital mortality and cumulative energy deficit

during first 4 days of ICU stay for 726 non-septic ICU patients



Reference is the measured resting energy expenditure of the patient

Weijs P. Crit Care 2014;18:701