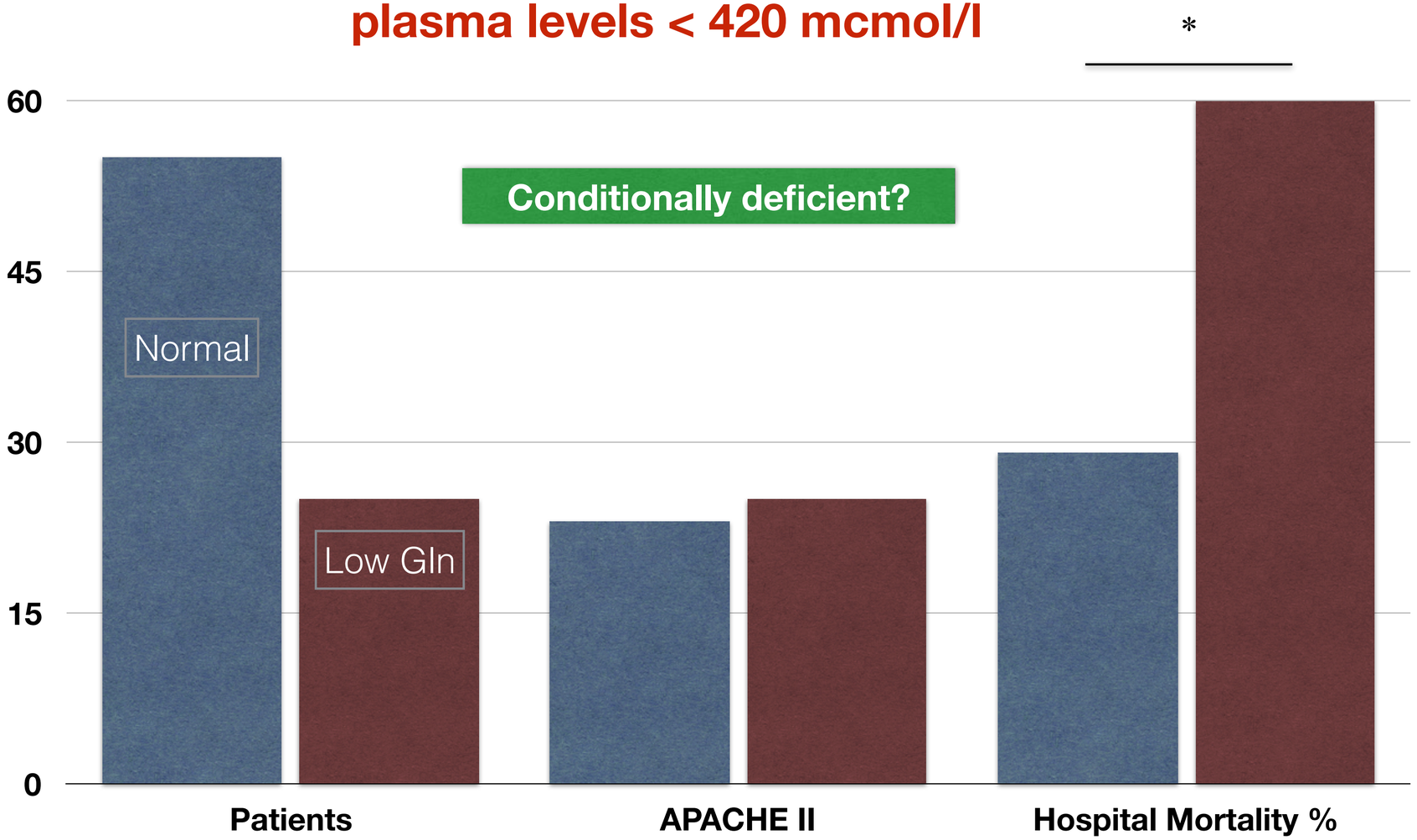
CRITICAL CARE NUTRITION ACADEMY

Is the hypothesis on glutamine deficiency still valid?

Arthur R.H. van Zanten, MD PhD
Internist-intensivist
Medical Manager Care Division
Gelderse Vallei Hospital
Ede, The Netherlands
E-mail: zantena@zgv.nl
www.criticalcarenutrition.nl

Mortality & baseline glutamine

plasma levels < 420 mcmol/l



Oudemans-van Straaten HM Intensive Care Med. 2001; 27(1):84-90

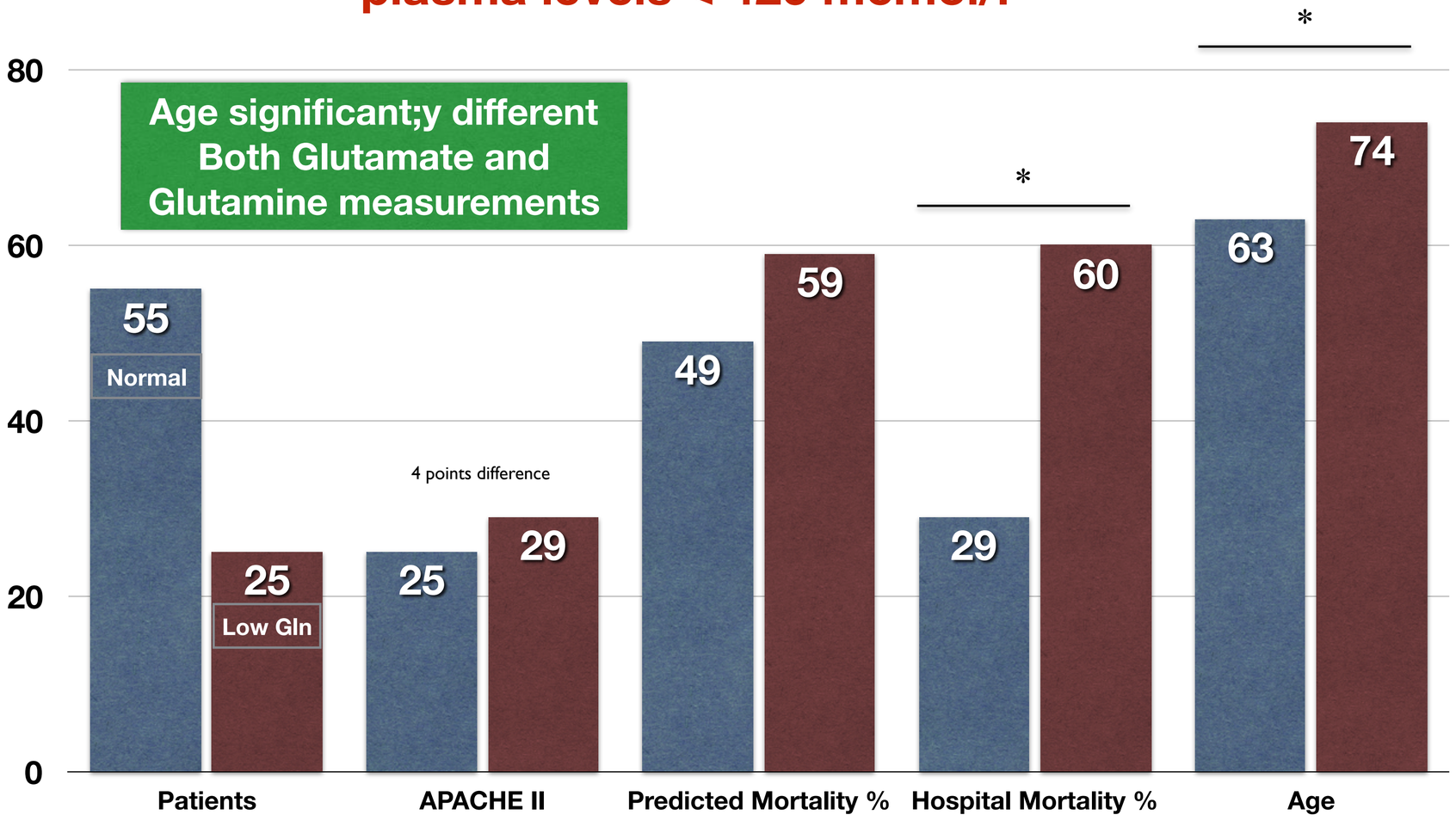
15 reasons to doubt the glutamine deficiency hypothesis

- Too simple concept
- Low plasma levels are inconsistent
- Sometimes high baseline levels
- No correlation disease severity
- Supplementation: no reduction endogenous production
- RCTs show harm
- High baseline glutamine associated with harm
- Conversion to citrulline and arginine
- No benefits in meta-analyses
- High-discharge glutamine associated with 1-year mortality
- Interaction with renal function
- Larger increase from baseline higher mortality
- Benefits only from older trials
- Benefits only from single center trials
- Low baseline associated with lower mortality

Van Zanten AR. Curr Opin Clin Nutr Metab Care. 2015 Mar;18(2):179-86.

Mortality & baseline glutamine

plasma levels < 420 mcmol/l



Oudemans-van Straaten HM Intensive Care Med. 2001; 27(1):84-90

Muscle protein

Protein catabolism

Amino acids

NH_4^+

glutamine synthetase

Glucose

glycolysis

Pyruvate

Glutamate

Glutamine

alanine aminotransferase

α-Ketoglutarate

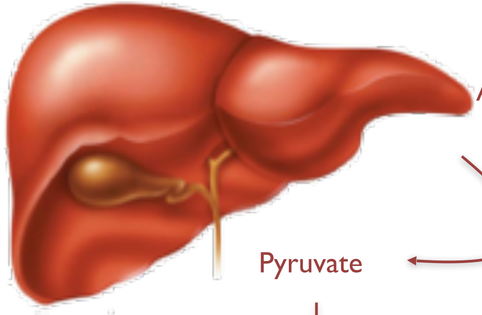
Alanine

Muscle compartment

Only liver and kidneys convert ammonia into urea. Ammonia is toxic to tissues. Excess ammonia is converted into nontoxic compounds as N-group carrier in blood to transport ammonia to the liver to be converted into urea.
Two carriers of N-groups in blood: glutamine and alanine.
Alanine and glutamine are released into the blood.
The liver absorbs alanine and and glutamine and deaminates it to reform pyruvate and glutamate.

Blood Alanine

Blood Glutamine



Alanine

Glutamine

glutaminase

α-Ketoglutarate

alanine aminotransferase

Pyruvate

Glutamate

gluconeogenesis

NH_4^+

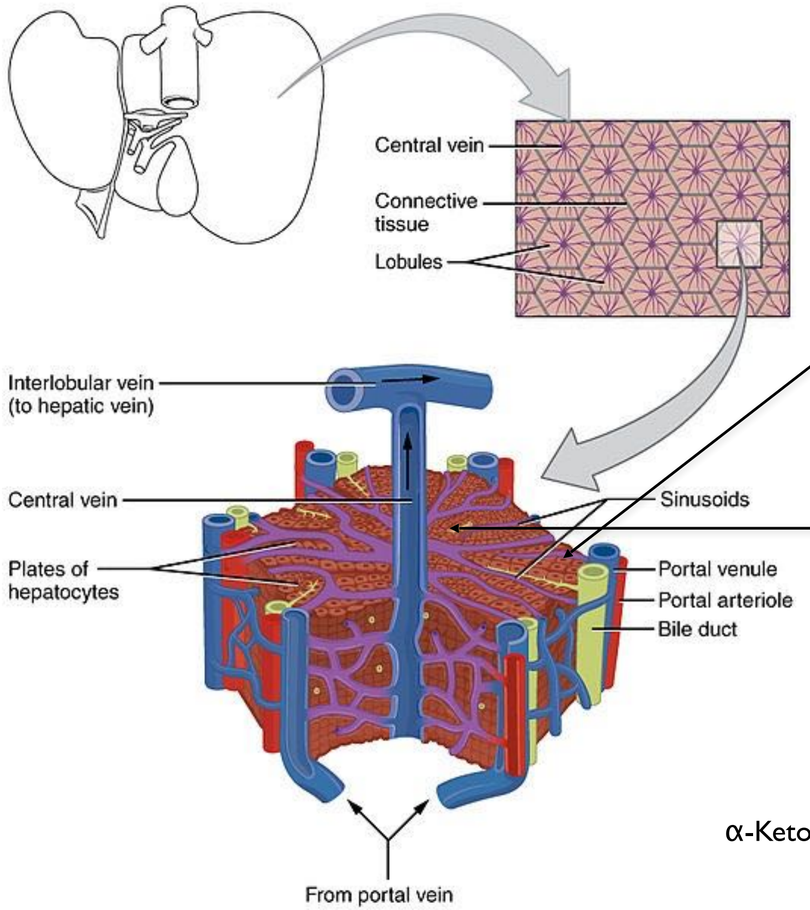
Urea cycle

Urea

Blood Glucose

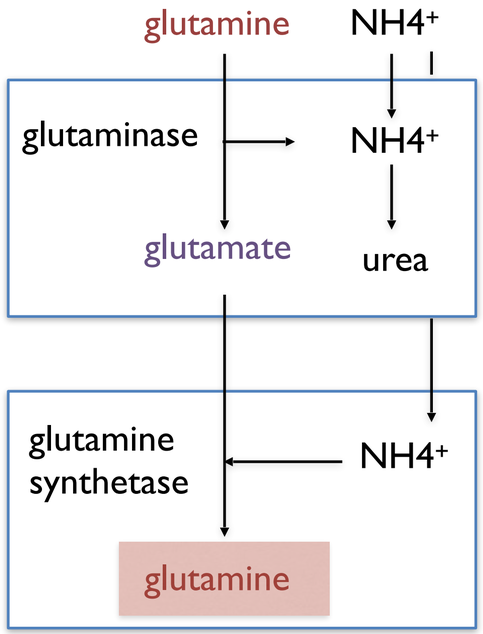
Glucose

Hepatic compartment



periportal cell

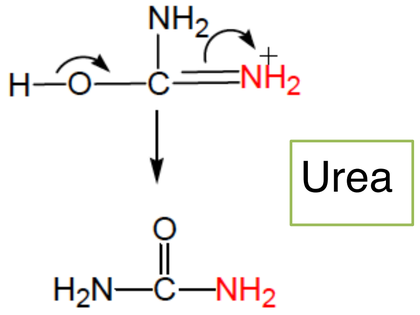
perivenous cell



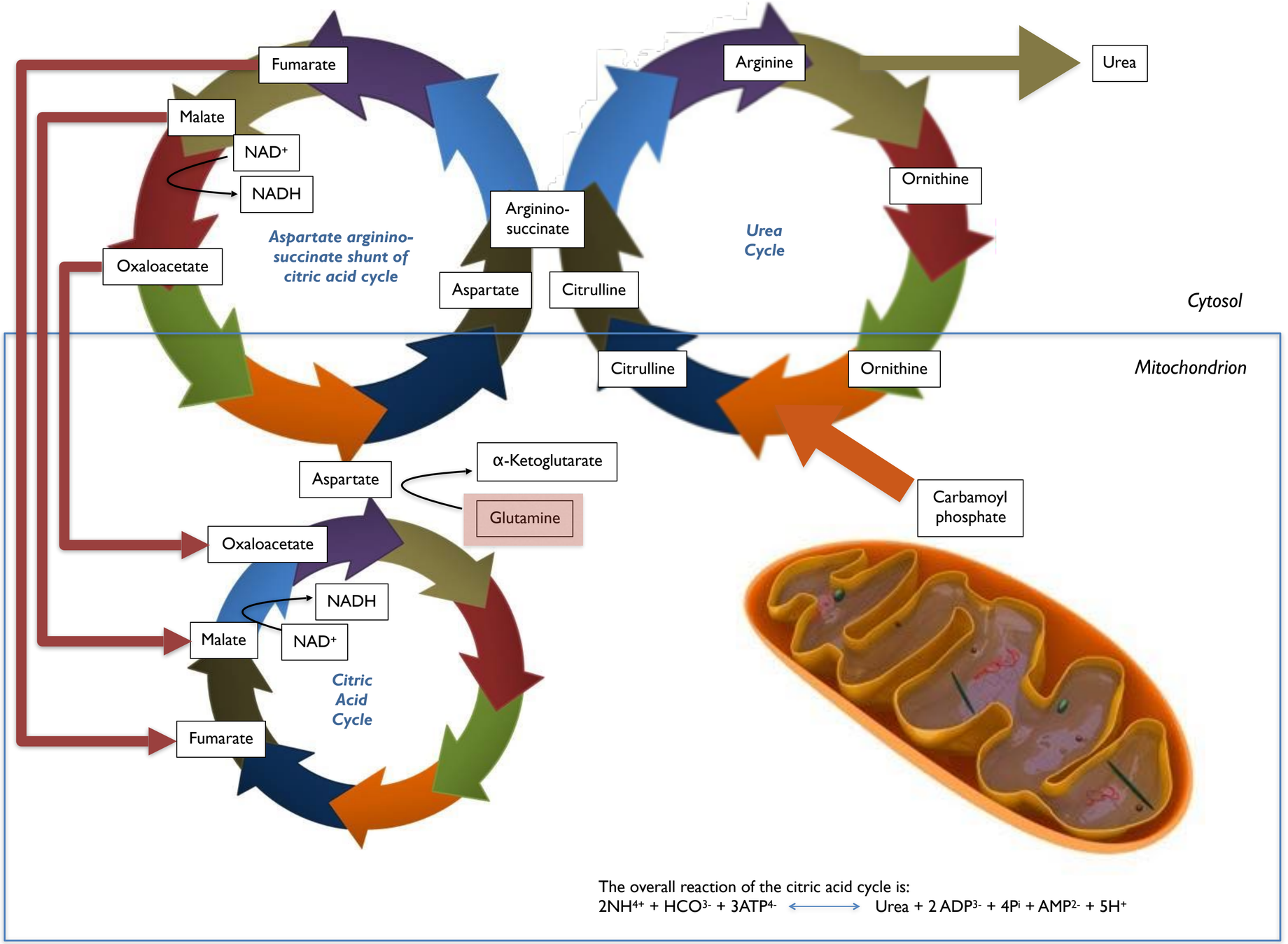
α-Ketoglutarate + NH^{4+} + NAD(P)H ⟷ Glutamate + $NAD(P)^{+}$

Glutamate + NH^{4+} +ATP ⟷ Glutamine + ADP + Pi

Glutamine synthetase uses ATP to activate glutamate for amination to form glutamine. High concentrations of ammonia deplete cells from ATP.



Urea



The overall reaction of the citric acid cycle is:

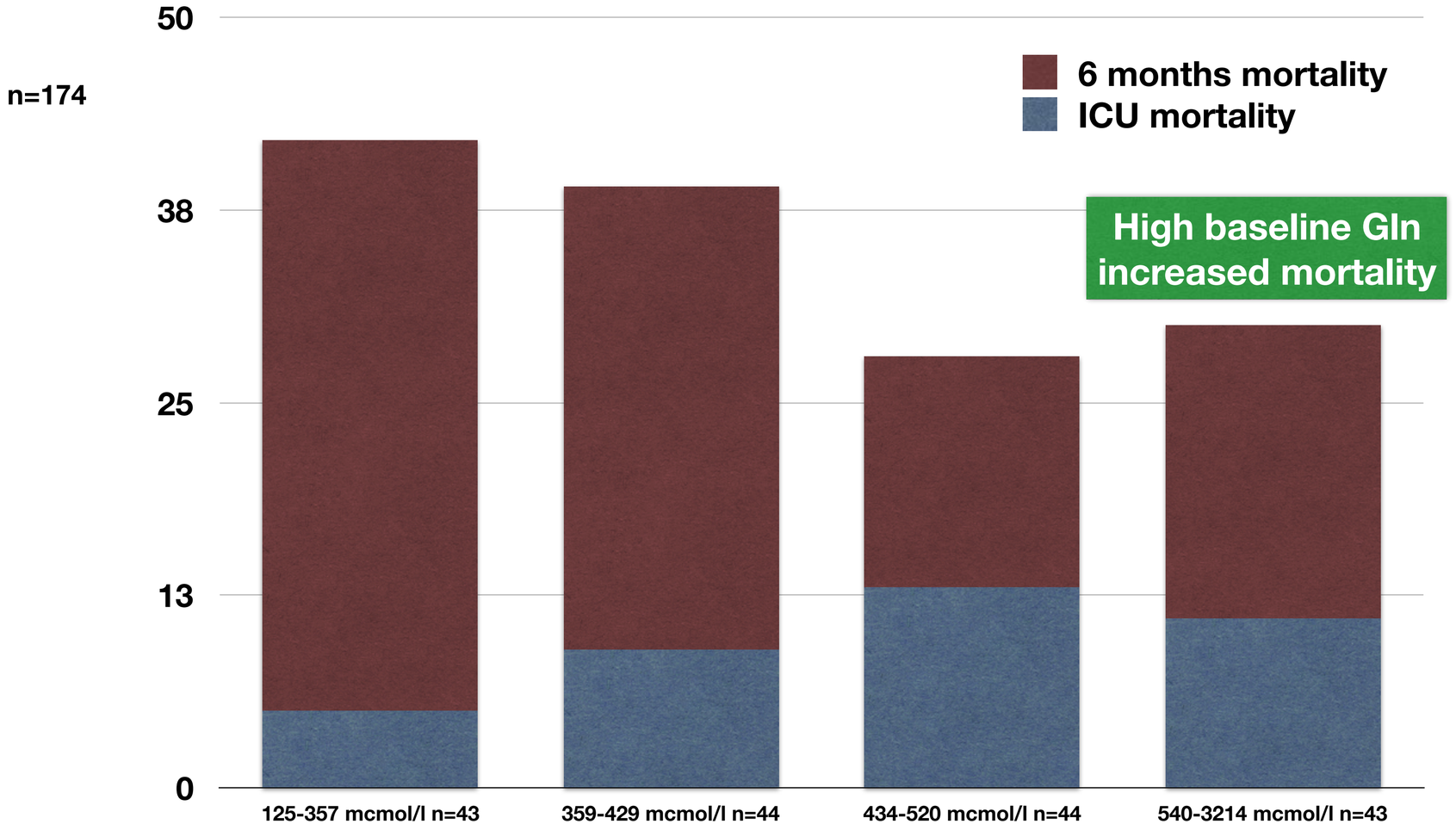
$2NH^{4+} + HCO^{3-} + 3ATP^{4-} \longleftrightarrow$ Urea + $2\,ADP^{3-} + 4P^{i} + AMP^{2-} + 5H^{+}$

Low baseline Gln inconsistent

- Large variations in numbers of ICU patients with low baseline plasma glutamine in clinical and experimental trials
- Varying from 0% to 75% of patients with baseline plasma Gln of < 420 mcmol/l

Wernerman J, et al. Acta Anaesth Scand. 2011; 55:812-8.
Heyland D, et al. N Engl J Med 2013; 368:1489-1497.
Van Zanten AR, et al. JAMA 2014; 312:514-524.22.
Berg A, et al. Amino Acids 2005; 29:221-228.
Berg A et al. Intensive Care Med 2006; 32:1741-6.
Carroll PV et al. Am J Physiol Endocrinol Metab 2004; 286:E151-157.
Engel JM, et al. Acta Anaesthesiol Scand 2003; 47:707-713.
Hirose T, et al. Clin Nutr 2014; 33:179-182.
Iresjö BM, et al. JPEN J Parenter Enteral Nutr 2006; 30:277-285.
Luo M, et al. Clin Nutr 2008; 27:297-306.
Palmer TE, et al. Nutrition 1996; 12:316-320.
Rodas PC, et al. Clin Sci (Lond) 2012; 122:591-597.
Tjäder I, et al. Intensive Care Med 2004; 30:266-275.
Vesali RF, et al. Clin Nutr 2002; 21:505-514.
Pérez-Bárcena J, et al. Crit Care 2010; 14:R233.

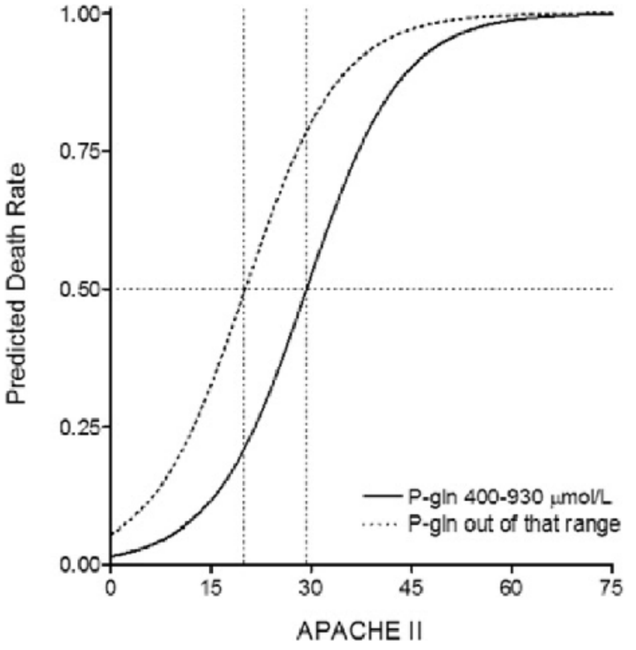
Gln baseline levels
6-months mortality U-shape?



Rodas, Wernerman. Clinical Science (2012) 122, 591–597

(a) Univariate analysis

	OR (CI)	P
Gln<420	2.02 (1.07–3.80)	0.029
Gln<400	2.41 (1.26–4.59)	0.007
Gln>930	4.11 (0.99–17.1)	0.043
Gln<400 or >930	3.22 (1.68–6.16)	<0.001
rGSH/tGSH>0.65	2.17 (1.07–4.40)	0.032
Gender (male)	1.35 (0.71–2.57)	0.36
APACHE (per point)	1.14 (1.09–1.21)	<0.001
Age (per year)	1.06 (1.03–1.08)	<0.001



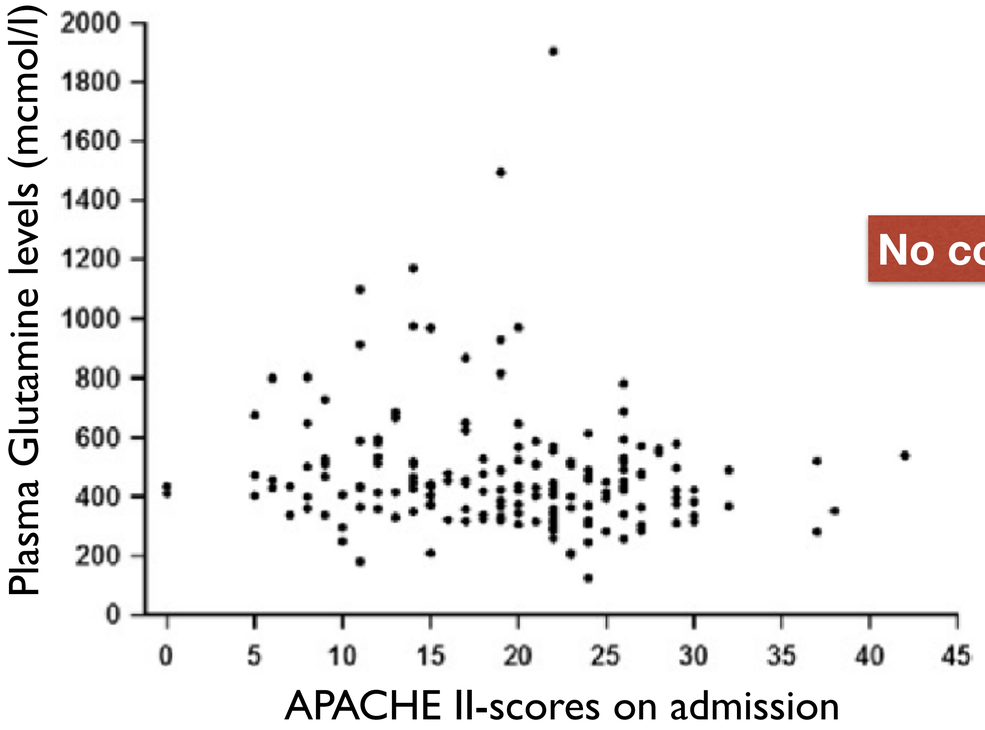
(b) Stepwise multiple logistic regression analysis

	β	OR (CI)	P	Correct (%)
Intercept	−6.43	0.002 (0.0002–0.016)		
APACHE (per patient)	0.13	1.14 (1.07–1.22)	<0.001	70.1
Gln <400 or >930	1.08	2.95 (1.38–6.32)	0.005	74.6
Age (per year)	0.04	1.04 (1.01–1.07)	0.006	78.1
rGSH/tGSH >0.65	0.85	2.35 (1.02–5.41)	<0.001	81.7

Rodas, Wernerman. Clinical Science (2012) 122, 591–597

No correlation baseline plasma Gln with severity of illness

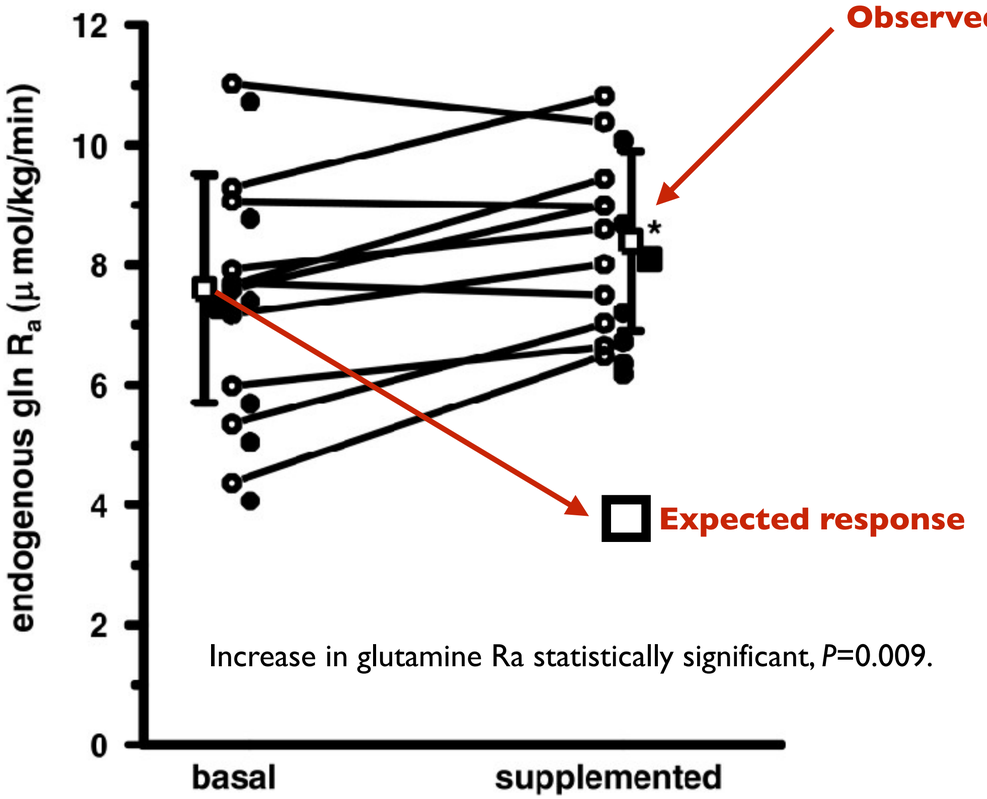
Consecutive patients admitted to the general ICU (n =174) at Karolinska Huddinge, Sweden



No correlation (P =0.46)

Rodas, Wernerman. Clinical Science (2012) 122, 591–597

Exogenous glutamine supplementation and endogenous glutamine production

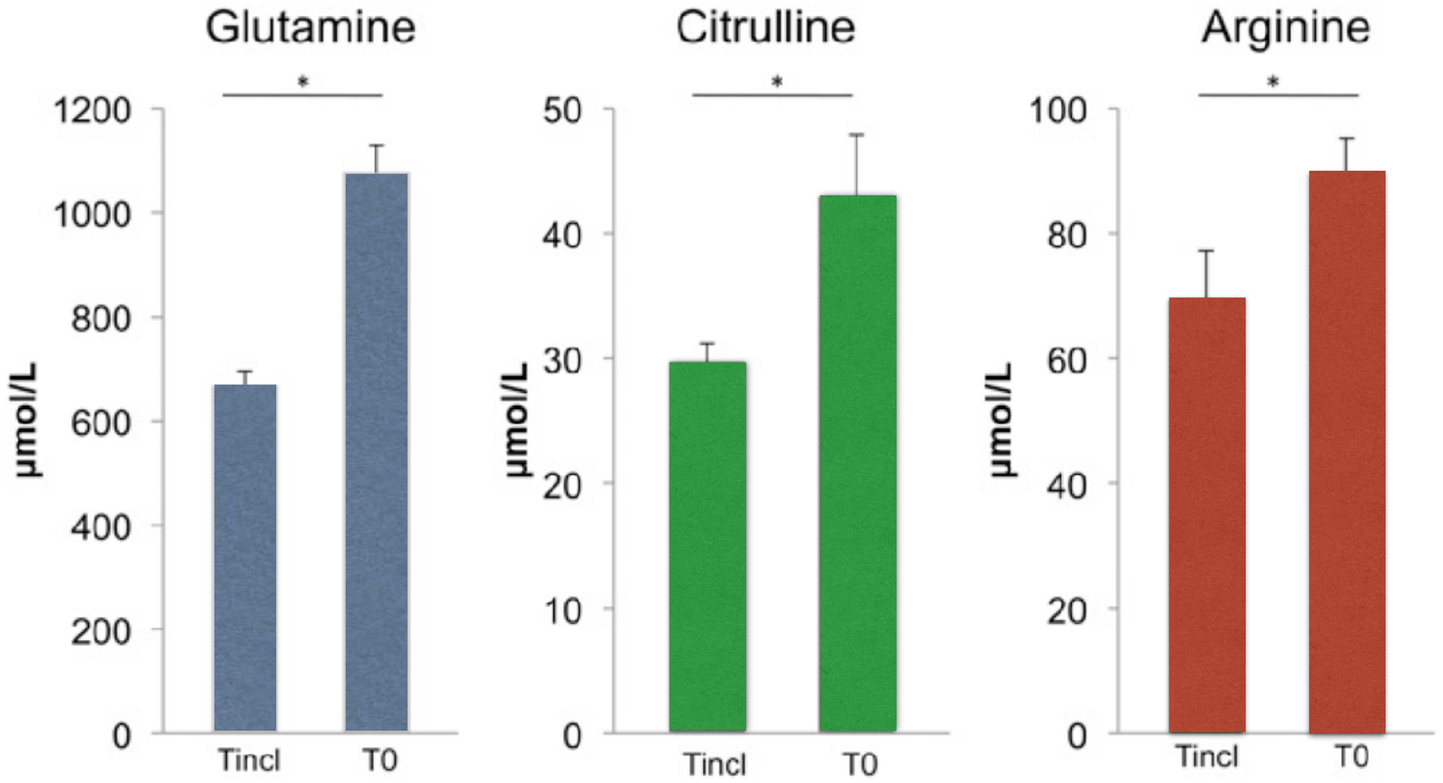


Increase in glutamine Ra statistically significant, *P*=0.009.

The hypothesized attenuation of endogenous glutamine production during L-alanyl-L-glutamine infusion given as a part of full nutrition was not seen.

Mori M. Critical Care 2014, 18:R72

Glutamine induced increases in citrulline and arginine



Mean (SEM) plasma concentrations of glutamine, citrulline, and arginine at TincI and after the administration of intravenous 0.5 g alanyl-glutamine/kg per day just before T0 (n = 7). Student's t test was used to determine significant differences in amino acid concentrations between TincI and T0.
*P , 0.05. TincI, time of inclusion; T0, start of the tracer infusion.

Buijs N et al. Am J Clin Nutr 2014;100:1385–91.

Plasma AA levels in sepsis

	Median plasma concentrations (maximum)	Median plasma concentrations (maximum)	P-value	Median plasma concentrations (minimum)	Median plasma concentrations (mimimum)	P-value
	Survivors	Non-survivors		Survivors	Non-survivors	
Glutamine	460.4	648.1	0.0074	415	361.5	0.289
Glutamate	60.6	41.8	0.0012	43.5	17.5	<0.0001
Methionine	26.9	42.5	0.0022	23.0	22.3	0.9209
Arginine	83.2	87.8	0.8345	64.5	46.6	0.019

High glutamine is associated with increased mortality

Toxicity

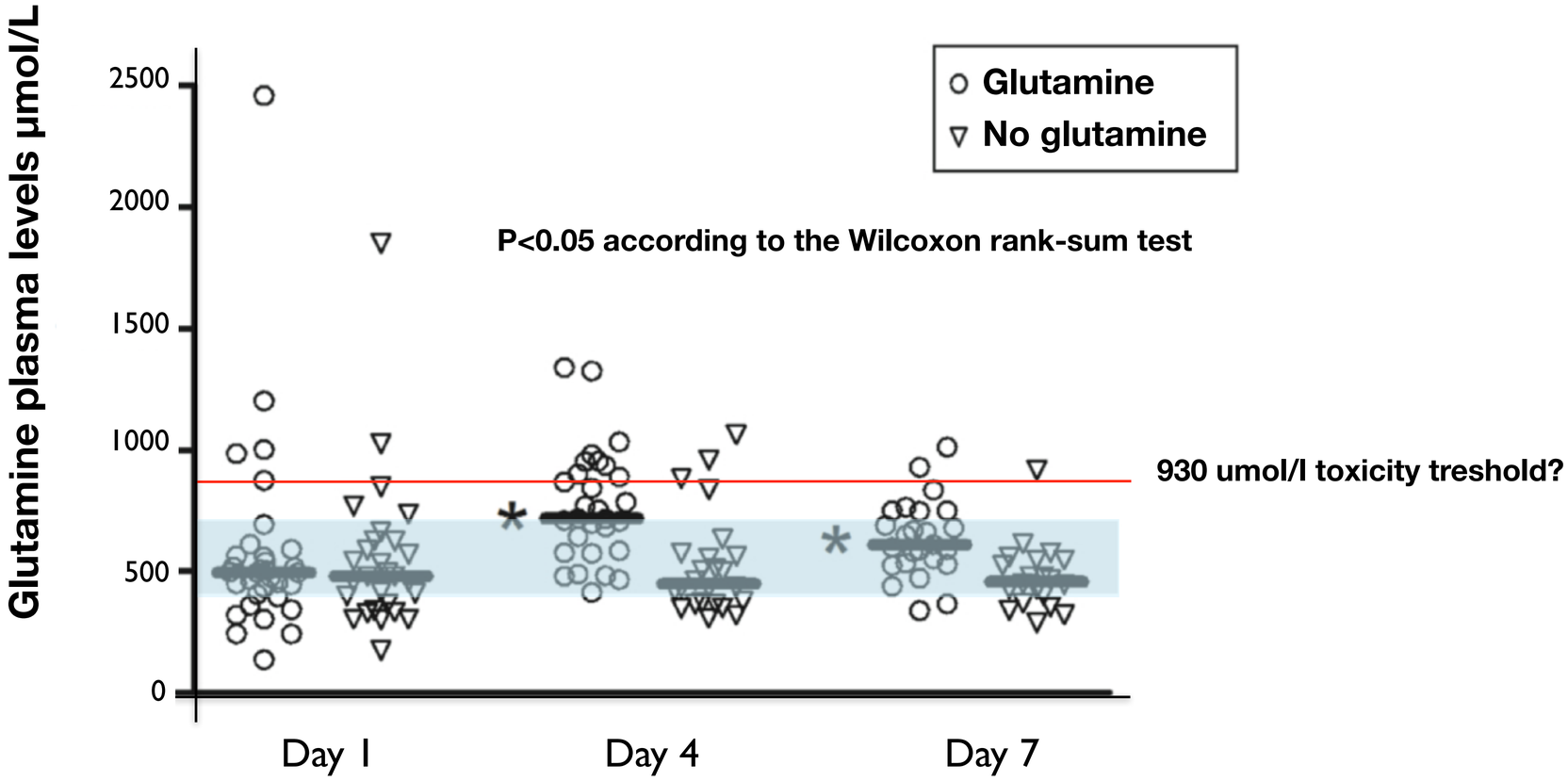
Worse Outcome

Non-survivors have lower minimum levels of glutamate and arginine and **non-survivors have higher maximum levels of glutamine** and methionine, and lower levels of glutamate

Hirose T. Clin Nutrition 2014;33:179-182

Glutamine levels

Normal range of glutamine: 420 – 700 umol/l



Heyland D. N Engl J Med 2013;368;16

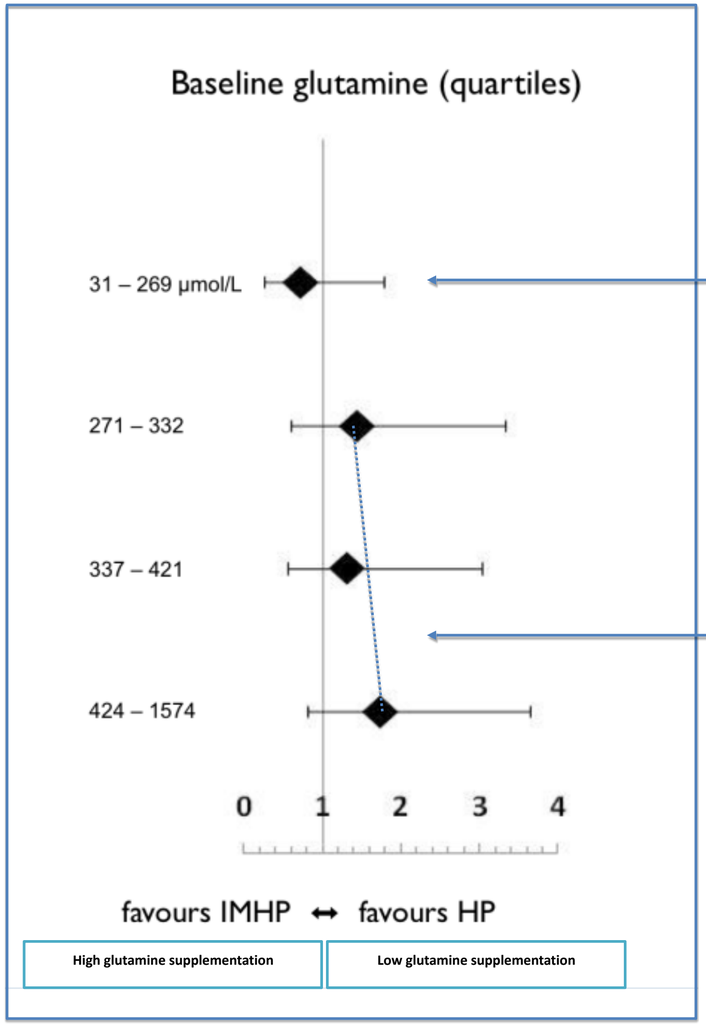
Treatment Effect on 28-d Mortality by Baseline Renal Dysfunction and Post-Baseline Dialysis

Multivariable Subgroup			OR (95% CI) compared to Placebo Arm		
Renal Dysfunction	Ever on Dialysis	Deaths – no. (%)	Glutamine	Antioxidants	Glutamine plus Antioxidants
No	No	158/634 (25)	1.1 (0.6-1.8)	1.1 (0.6-1.8)	1.3 (0.8-2.2)
No	Yes	58/142 (41)	0.4 (0.2-1.2)	0.5 (0.2-1.3)	0.6 (0.3-1.6)
Yes	No	76/240 (32)	**3.9 (1.7-9.0)**	**3.3 (1.4-7.8)**	1.6 (0.7-3.8)
Yes	Yes	71/202 (35)	1.8 (0.7-4.4)	1.4 (0.6-3.5)	**3.1 (1.2-7.6)**

Cells in bold indicate treatment arm had significantly higher 28 day mortality than placebo at P < 0.05.

Heyland DK, et al. JPEN J Parenter Enteral Nutr. 2014 May 5

Metaplus baseline glutamine levels effect on 6-months mortality



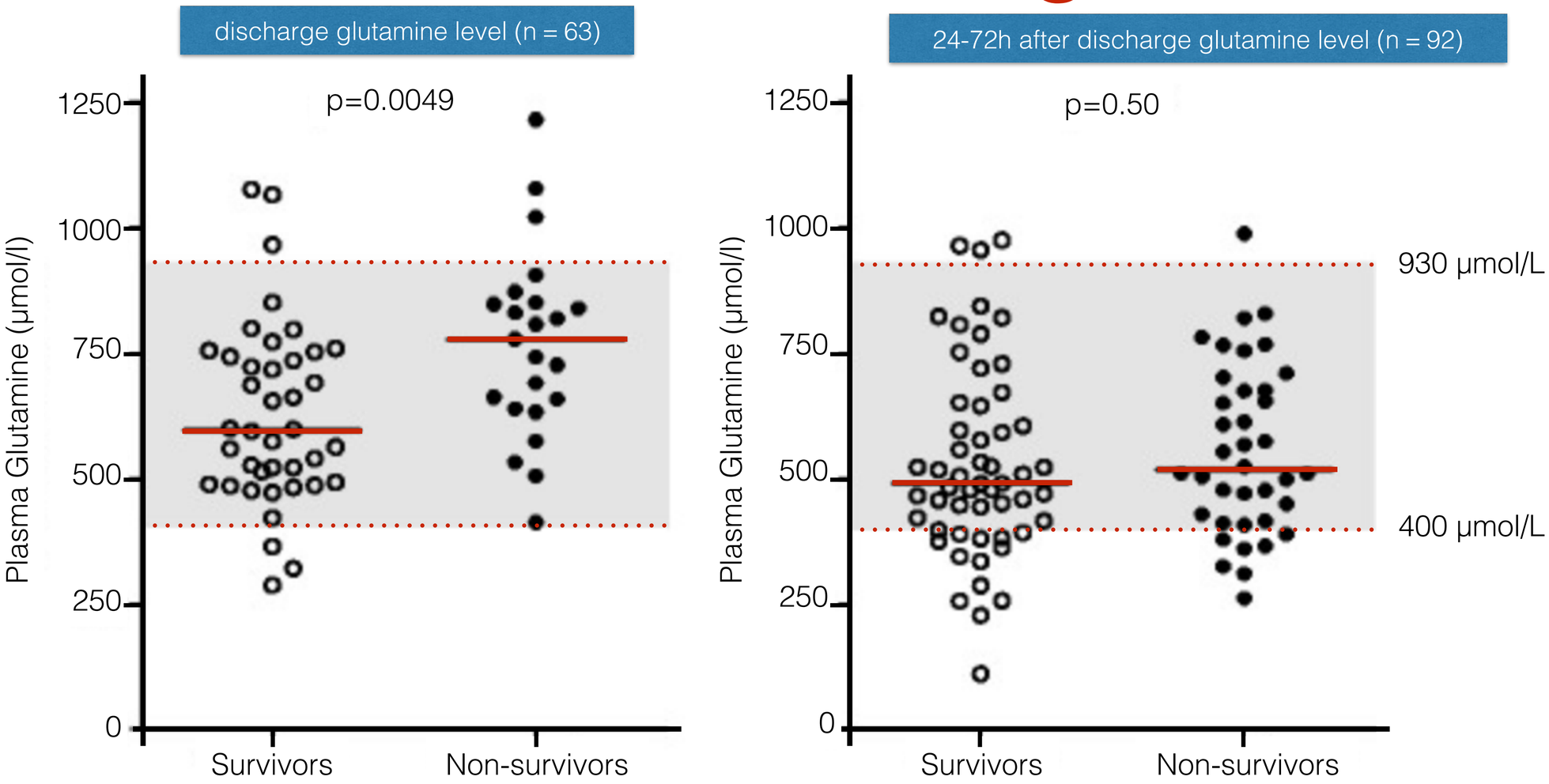
75% of patients have low glutamine levels at baseline (<421 mcmol/l)

No better outcome in patients with very low baseline glutamine levels (<31 – 269 mcmol/l)

trend towards poorer outcome in patients with higher baseline glutamine levels

Van Zanten AR et al. JAMA 2014 Aug 6;312(5):514-24.

Glutamine concentrations at ICU discharge



Fully fed ICU patients IV glutamine for >3 days at ICU discharge and post-ICU.

Smedberg M, Crit Care 2014 18:677

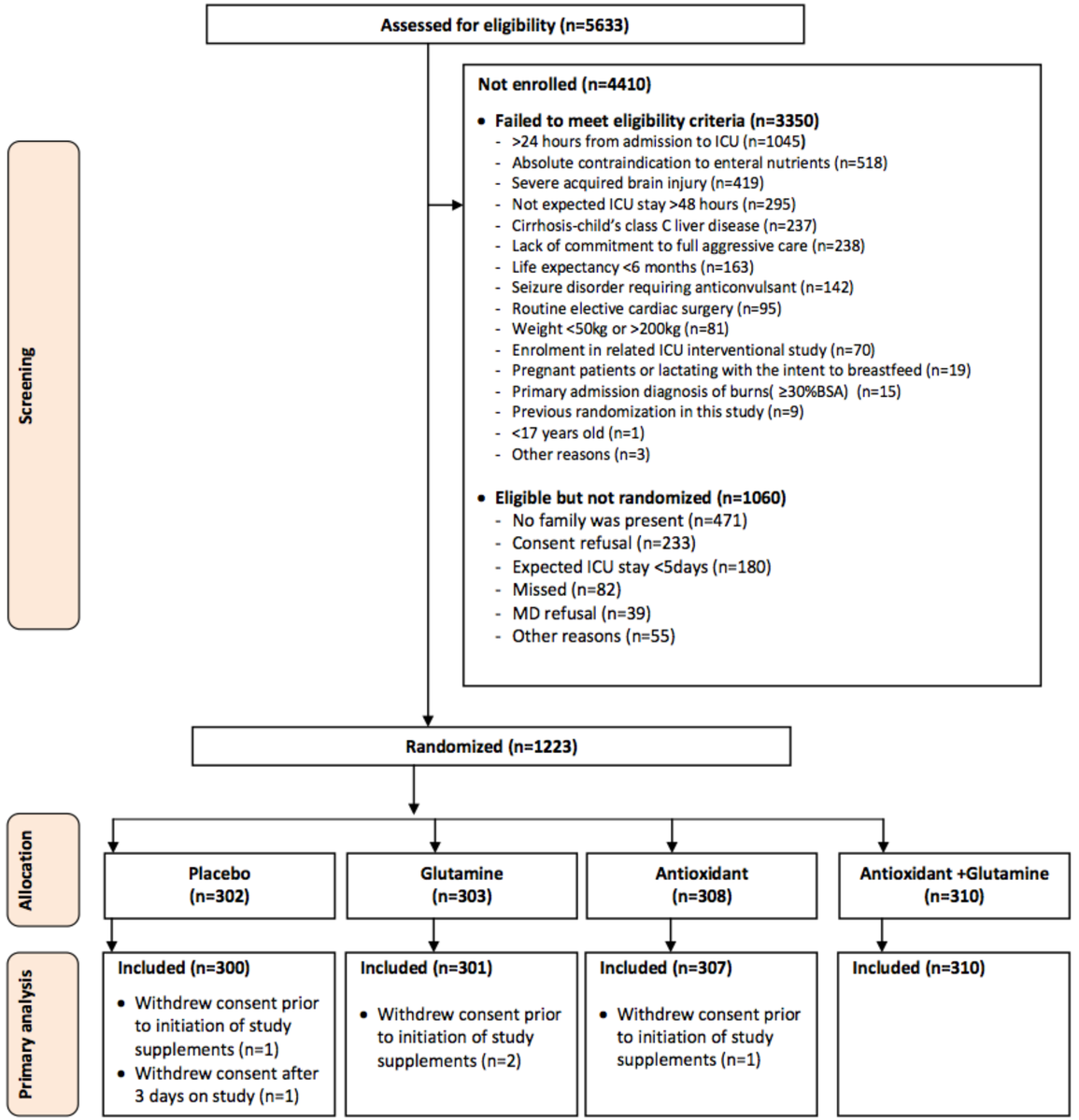
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Glutamine and Antioxidants in Critically Ill Patients

Daren Heyland, M.D., John Muscedere, M.D., Paul E. Wischmeyer, M.D., Deborah Cook, M.D., Gwynne Jones, M.D., Martin Albert, M.D., Gunnar Elke, M.D., Mette M. Berger, M.D., Ph.D., and Andrew G. Day, M.Sc., for the Canadian Critical Care Trials Group

Factorial Design
Placebo 302 patients
Glutamine 303 patients
Antioxidant 308 patients
Antioxidant+glutamine 310 patients



Heyland D. N Engl J Med 2013;368;16

Mortality 6 months after glutamine supplementation

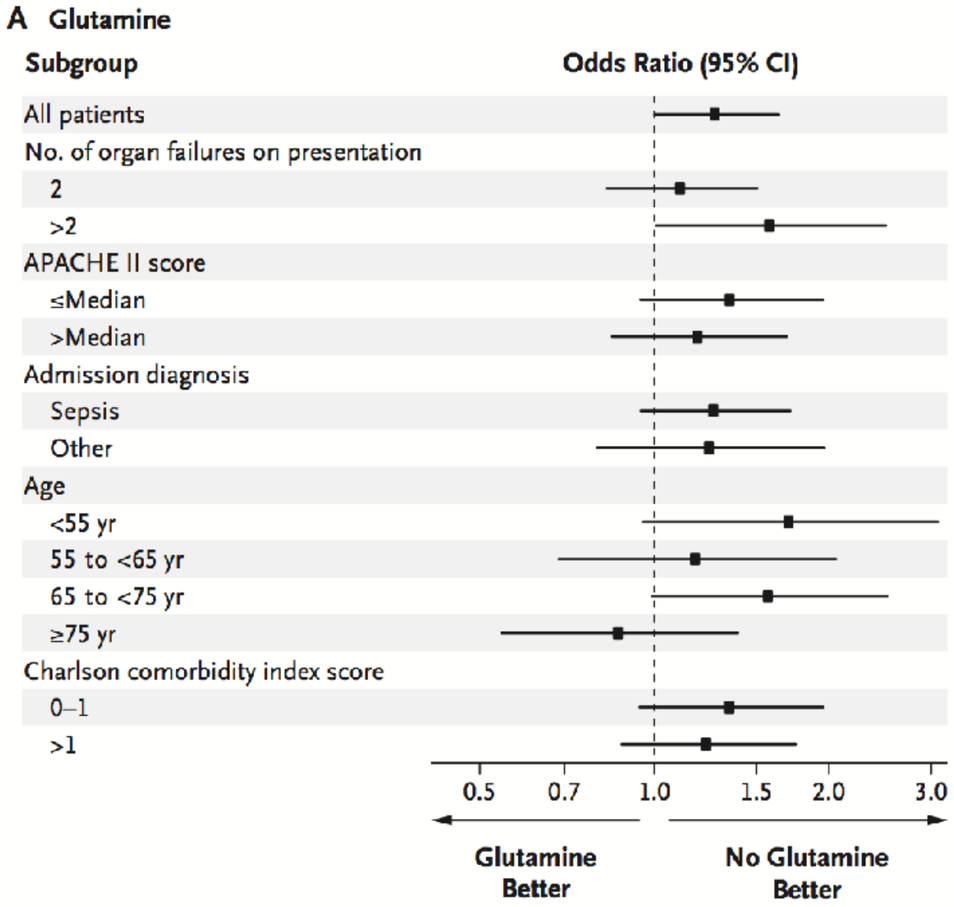
Table 2. Odds Ratio for Death According to Study Agent.*

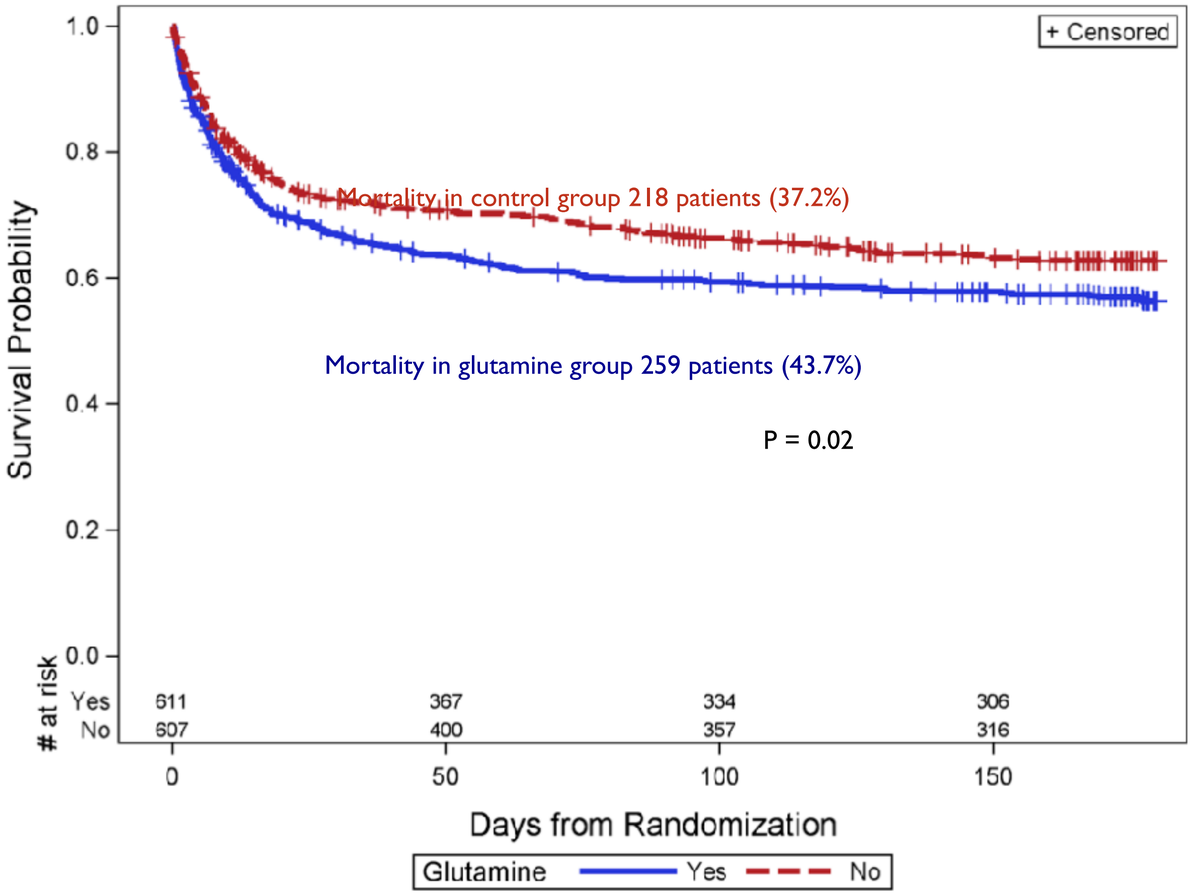
Variable	Antioxidants		Glutamine-Specific Odds Ratio with Antioxidants (95%)	Overall Adjusted Odds Ratio with Antioxidants (95% CI)	P Value
	Yes	No			
Glutamine				1.09 (0.86–1.40)	0.48
Yes — no. of patients who died/total no. (%)	101/310 (32.6)	97/301 (32.2)	1.02 (0.72–1.43)		
No — no. of patients who died/total no. (%)	89/307 (29.0)	76/300 (25.3)	1.20 (0.84–1.72)		
Antioxidant-specific odds ratio with glutamine (95% CI)	1.18 (0.83–1.66)	1.40 (0.98–2.00)			
Overall adjusted odds ratio with glutamine (95% CI)		1.28 (1.00–1.64)			0.05†

No effect in antioxydant group on mortality

Heyland D. N Engl J Med 2013;368;16

Mortality 6 months after glutamine supplementation

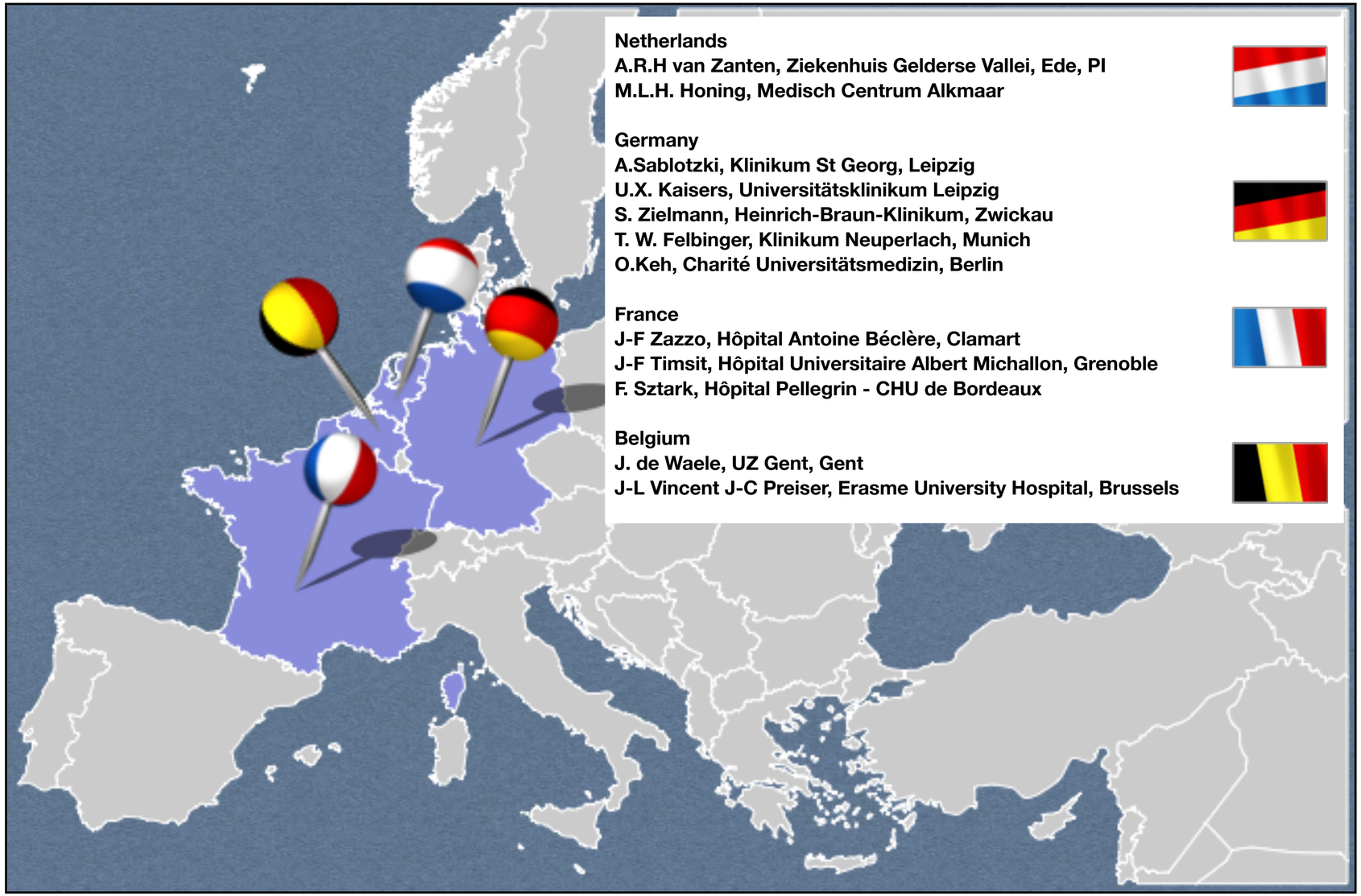




No statistical differences in infections

Heyland D. N Engl J Med 2013;368;16

MetaPlus Study



Van Zanten AR et al. JAMA 2014 Aug 6;312(5):514-24.

Product compositions

during ICU stay up to maximum of day 28

Nutrients (per 1500 mL)	IMHP	HP
Energy	1920 kcal	1920 kcal
Protein (g) ▪ Cas/ wheat hydr / Ala-Gln ▪ Glutamine	112.5 g (23.4 En%) ▪ ~~41% / 39% / 20%~~ ▪ 30 g	112.5 g (23.4 En%) ▪ 100 %/0/0 ▪ 9 g
Carbohydrates ▪ Fructose	141 g - (29.3 En%) ▪ 0 g	231 g - (48 En%) ▪ 0 g
Fat ▪ MCT ▪ EPA – DHA	96 g (45 En%) ▪ ~~19.5 g~~ ▪ 7.5 g	55.5 g (26.3 En%) ▪ 0 g ▪ 0 g
Anti-oxidants ▪ vitamin C ▪ vitamin E (alpha toco) ▪ Selenium ▪ Zinc	Above normal values ▪ 690 mg ▪ 266 mg (400 IU) ▪ 285 mcg ▪ 30 mg	Normal values ▪ 195 mg ▪ 22.5 mg ▪ 112.5 mcg ▪ 22.5 mg
Other Vit / Min./ trace el.	Normal values	Normal values
Fiber	22.5 g (2.3 En%)	22.5 g (2.3 En%)

Van Zanten AR et al. JAMA 2014 Aug 6;312(5):514-24.

Incidence new infections

Primary Outcome Measure	IMHP	HP	P value
	n=152	n=149	
All	**53%**	**52%**	0.961
Medical (IMHP n=54 vs. Protison n=55)	**39%**	**47%**	0.377
Surgical (IMHP n=81 vs. Protison n=75)	**62%**	**51%**	0.164
Trauma (IMHP n=55 vs. Protison n=54)	**58%**	**67%**	0.361

- % of subjects with at least one infection after start study product, using CDC-infection criteria
- No statistical significant differences between IMHP and Protison based on Chi square tests.

Van Zanten AR et al. JAMA 2014 Aug 6;312(5):514-24.

Mortality

	28-days mortality Incidence (%)		
	IMHP	HP	p value
All (n=168)	**20%**	**17%**	0.420
Medical (n=109)	**35%**	**24%**	0.186
Surgical (n=156)	**14%**	**16%**	0.670
Trauma (n=109)	**7%**	**4%**	0.679

	6-months mortality Incidence (%)		
	IMHP	HP	p value
All (n=297)	**35%**	**28%**	0.212
Medical (n=109)	**54%**	**35%**	0.044
Surgical (n=152)	**27%**	**28%**	0.900
Trauma (n=107)	**15%**	**17%**	0.759

Differences between IMHP and HP based on Chi square tests.

Van Zanten AR et al. JAMA 2014 Aug 6;312(5):514-24.

6-months mortality
Cox hazard model

After predefined covariates were tested in univariate analysis

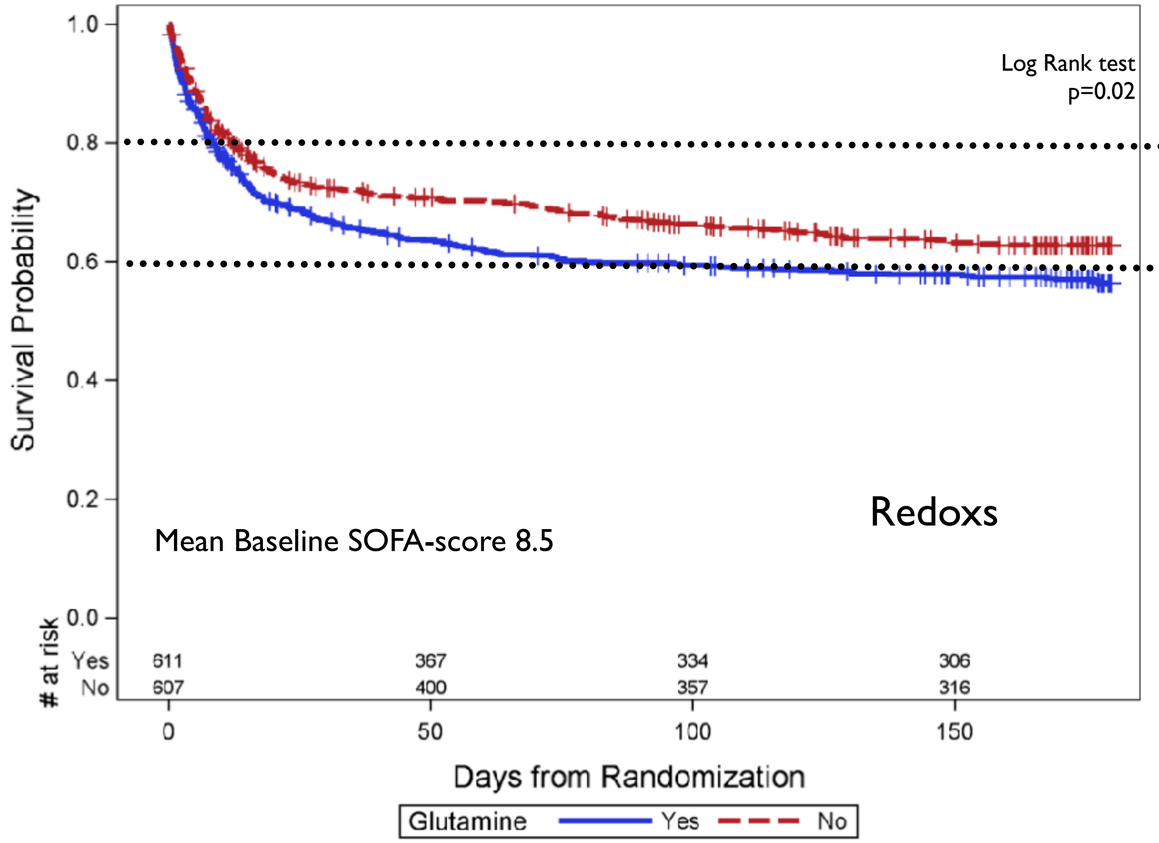
	Hazard Ratio	Lower Limit	Upper Limit	P value
IMHP vs. Protison	1.57	1.03	2.39	0.036
Age (70-80 vs. age (>80)	0.47	0.27	0.81	0.006
Age (50-70) vs. age (>80)	0.24	0.14	0.43	<0.001
Age (<50) vs. age (>80)	0.12	0.05	0.27	<0.001
APACHE-II score (unit)	1.05	1.02	1.09	<0.001

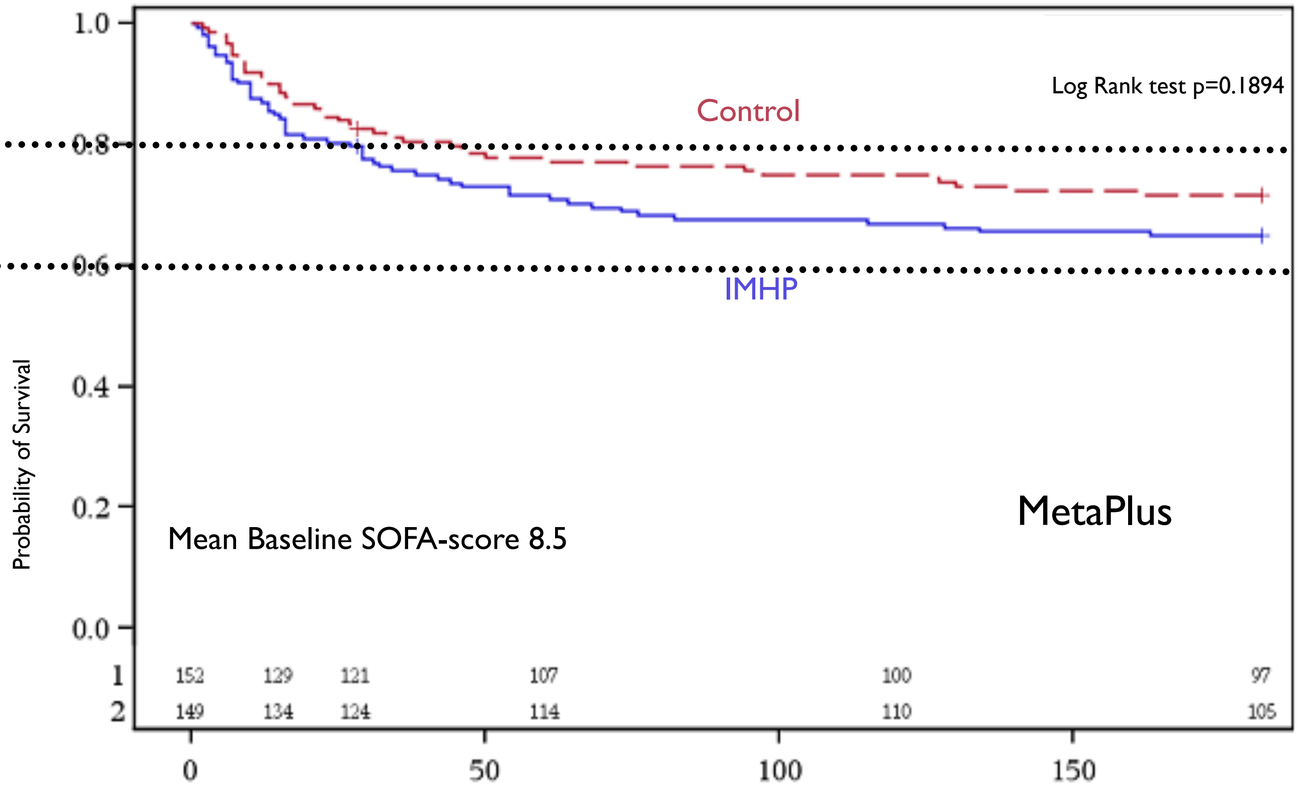
After adjustment for age and APACHE-II score,
risk of death is 57% higher for patients on IMHP versus control feed patients (P=0.036)

pre-defined covariates: age (≤50, 51-70, 71-80, >80 yrs), sex, BMI, APACHE-II score, adj. pred. mortality, screening SOFA score, baseline glutamine, baseline glucose, type of patient (medical, surgical non trauma, surgical trauma, trauma non surgical), start study product since ICU admission, occurrence of pre-existing infection, and treatment with antibiotics at start of study. The final model was constructed using univariate screening followed by a stepwise variable-selection procedure.

Van Zanten AR et al. JAMA 2014 Aug 6;312(5):514-24.

6-months survival probability: MetaPlus and Redoxs

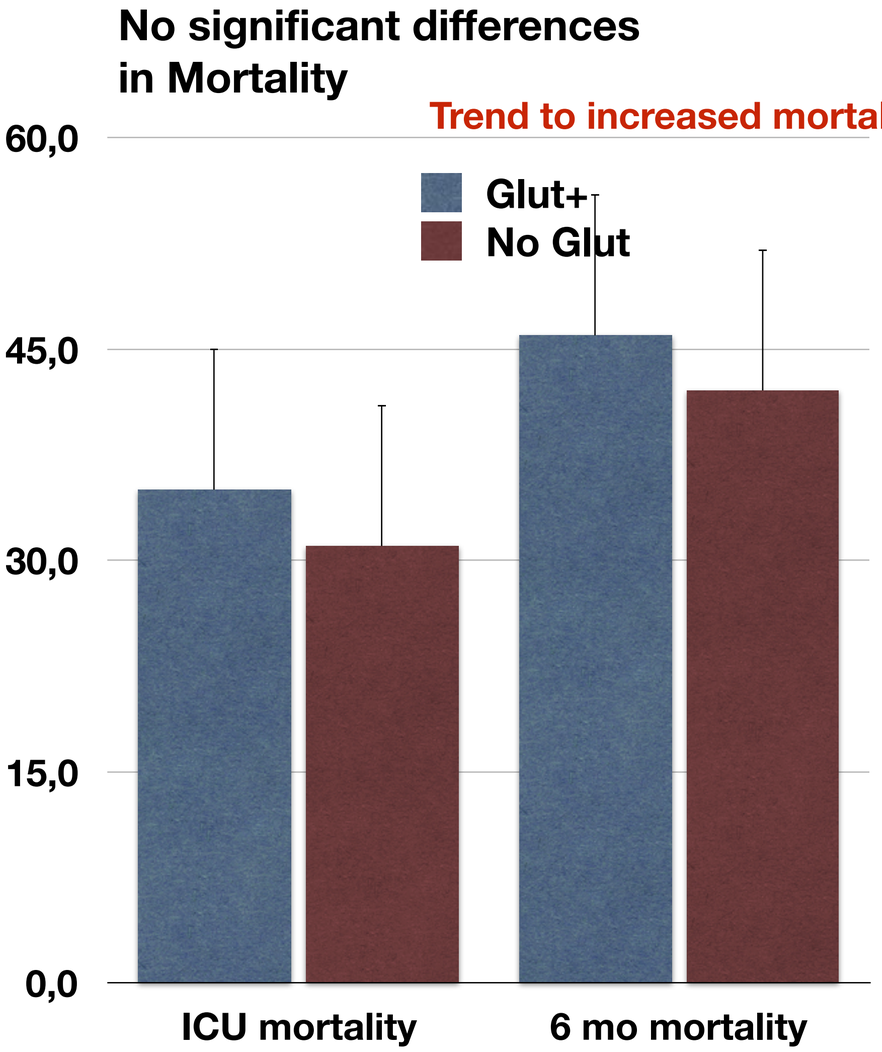


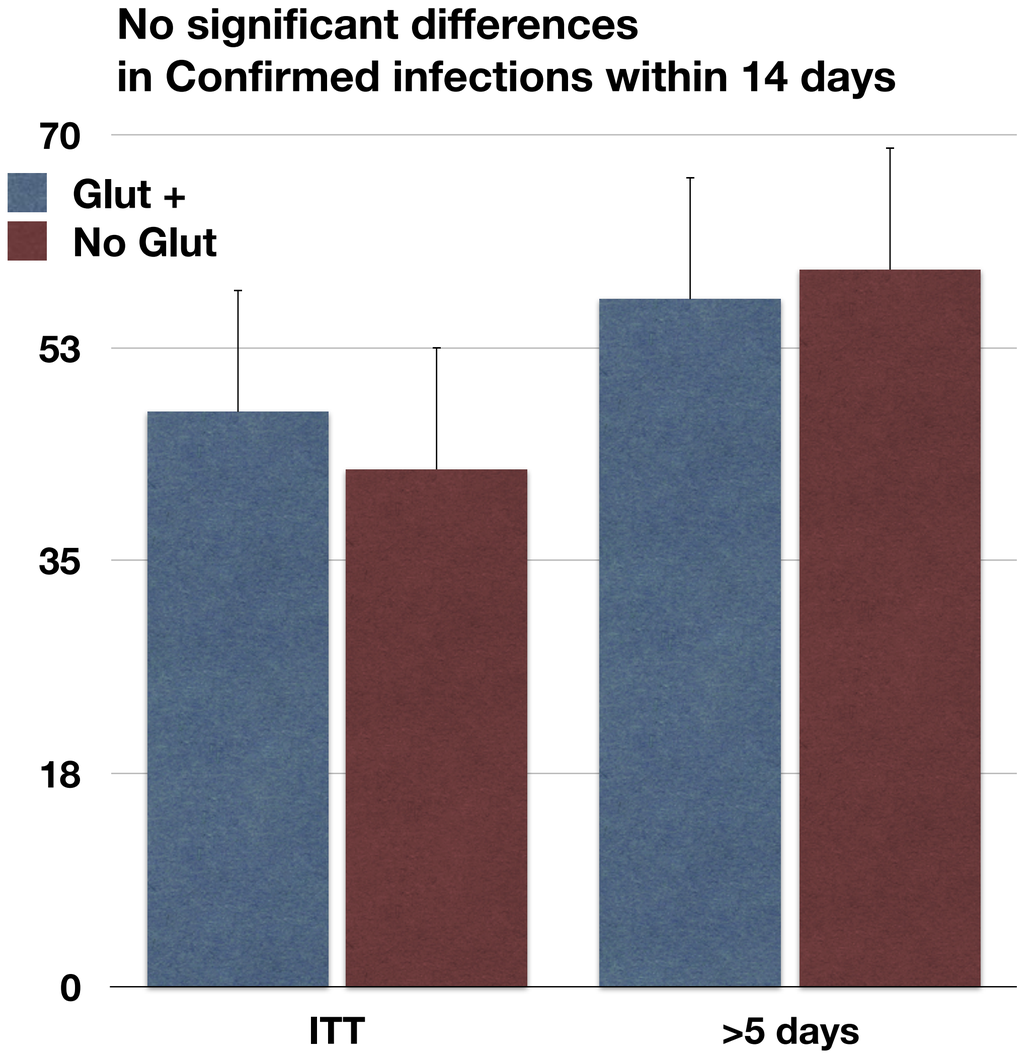


Comparing IMHP&HP groups in the MetaPlus trial the hazard ratio for 6-month mortality adjusted for age and APACHE-II score is 1.57 (95%CI, 1.03-2.39; P = .04).

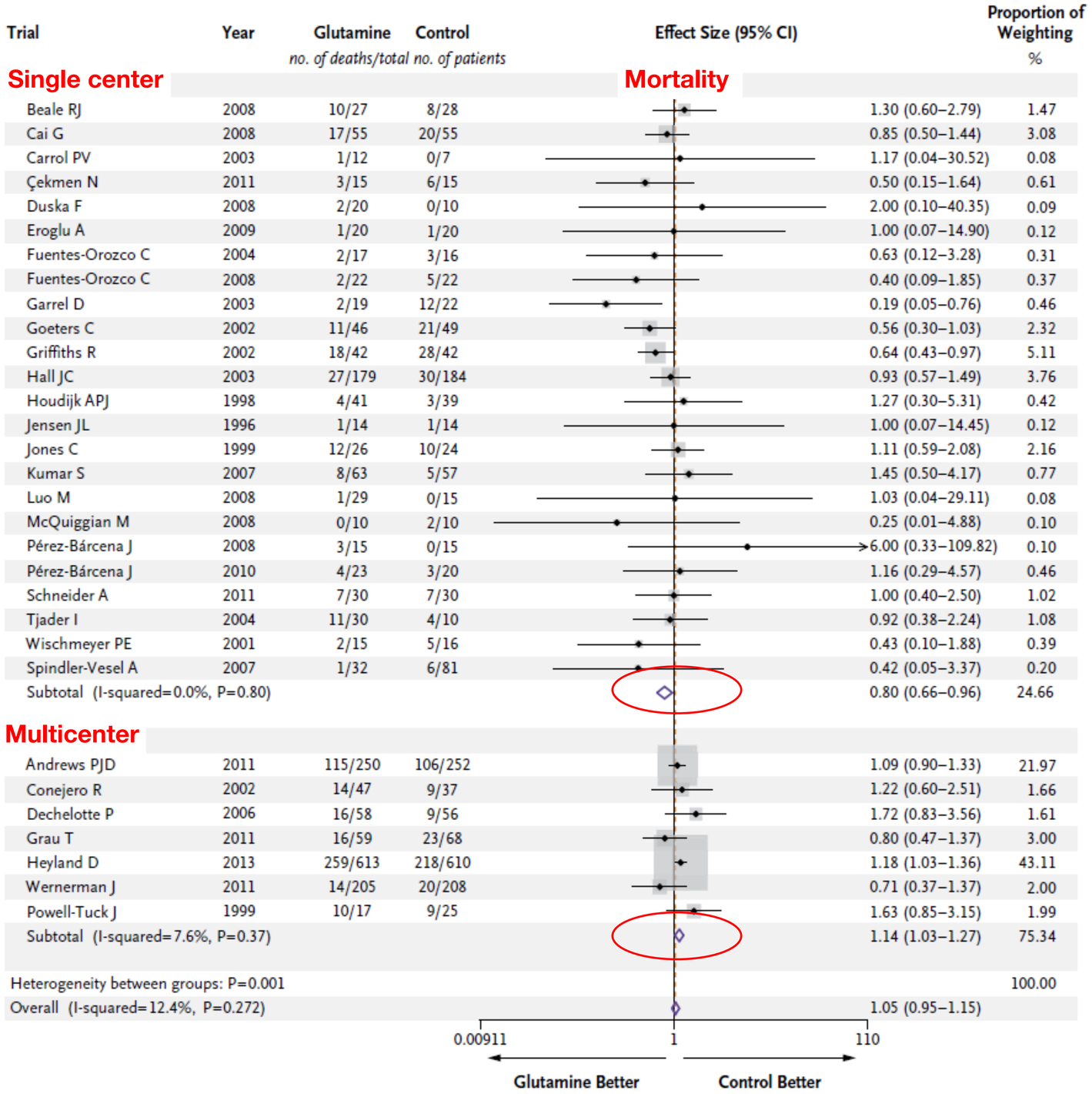
Redoxs trial Data with permission D. Heyland
Van Zanten AR et al. JAMA 2014 Aug 6;312(5):514-24.

The SIGNET Trial





P Andrews: Scottish Intensive Care Glutamine or seleNium Evaluative Trial: 2010



= 0.015).

Pausin L et al. New Engl J Med 2013

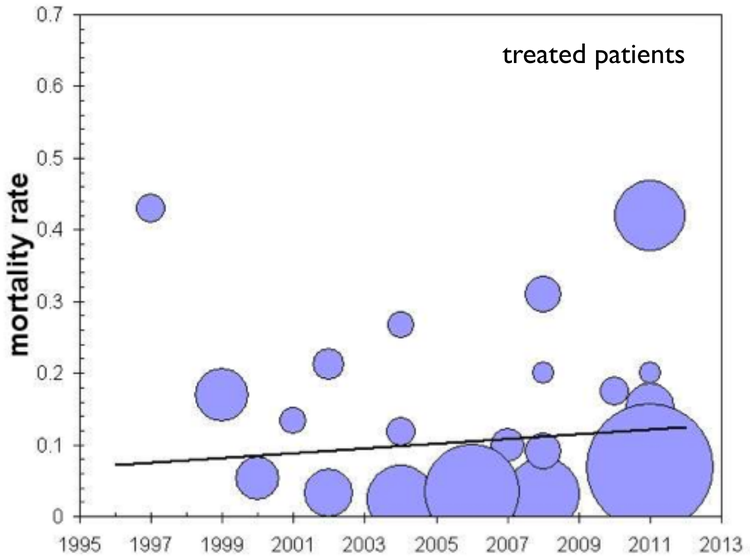
Overall mortality PN GLN trials

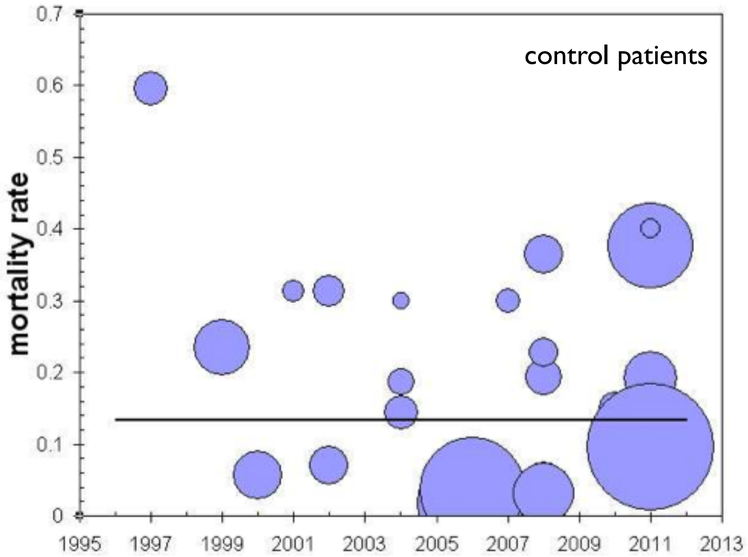
Subgroup analysis	Number of trials	Number of patients	Effect on overall mortality [RR (95% CI), p]	Test for subgroup differences
Single center	19	1011	0.75 (0.60, 0.93), P=0.009	P=0.04
Multi-center	5	1306	1.03 (0.83,1.28) P=0.79	

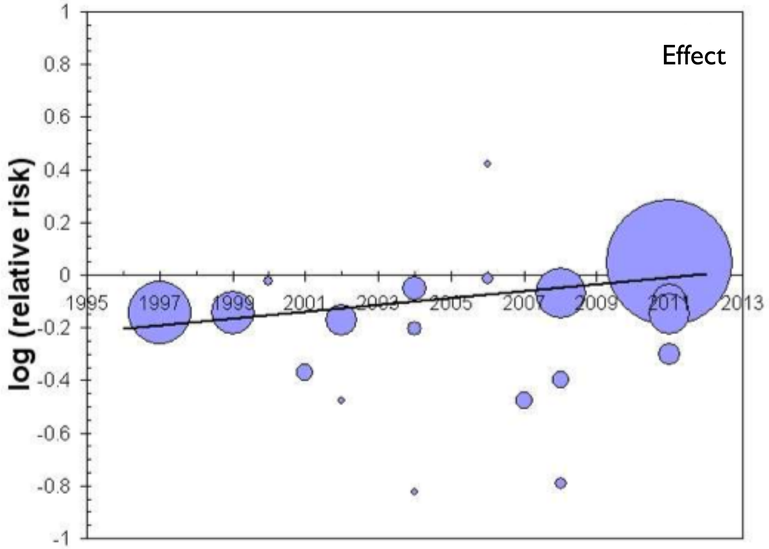
Because of a concern about 'single-center' bias, these investigators showed that only the single center trials demonstrated a significant effect of glutamine on overall and hospital mortality and infectious outcomes with no beneficial effect observed in the multicenter trials.

Wischmeyer P et al. Critical Care 2014, 18:R76

Meta-regression analysis of temporal trends (1995-2012) of mortality in patients given parenteral glutamine supplementation or controls not receiving this supplementation.







REDOXS and MetaPlus not included

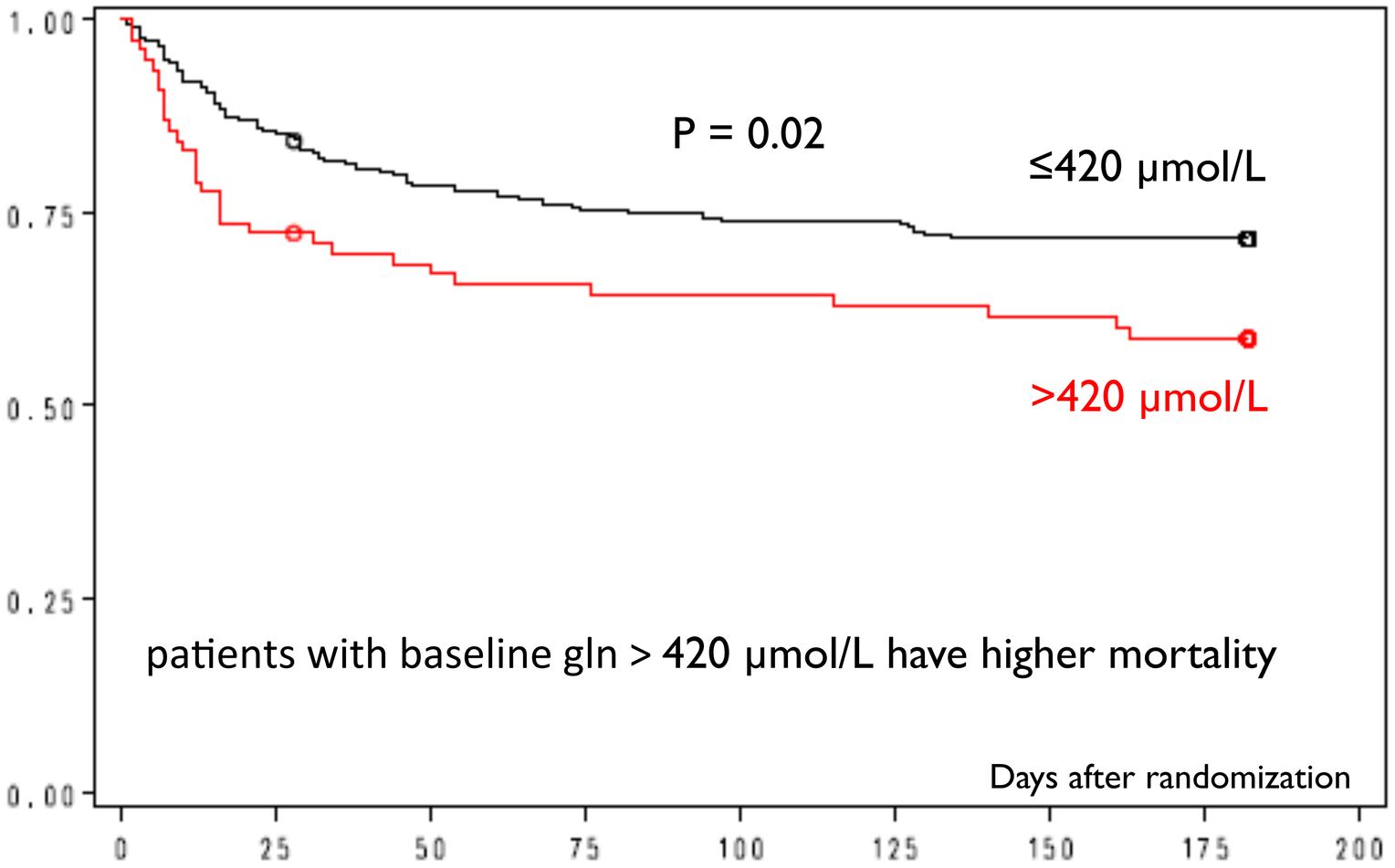
time-course of the RR risk for the comparison of glutamine supplementation versus no-glutamine

Mortality reduction of parenteral glutamine has vanished over time

Maratea D. et al. Clinical Nutrition 2013 (33);4:735-736

Survival & baseline Gln

(baseline, cut-off 420 µmol/L)

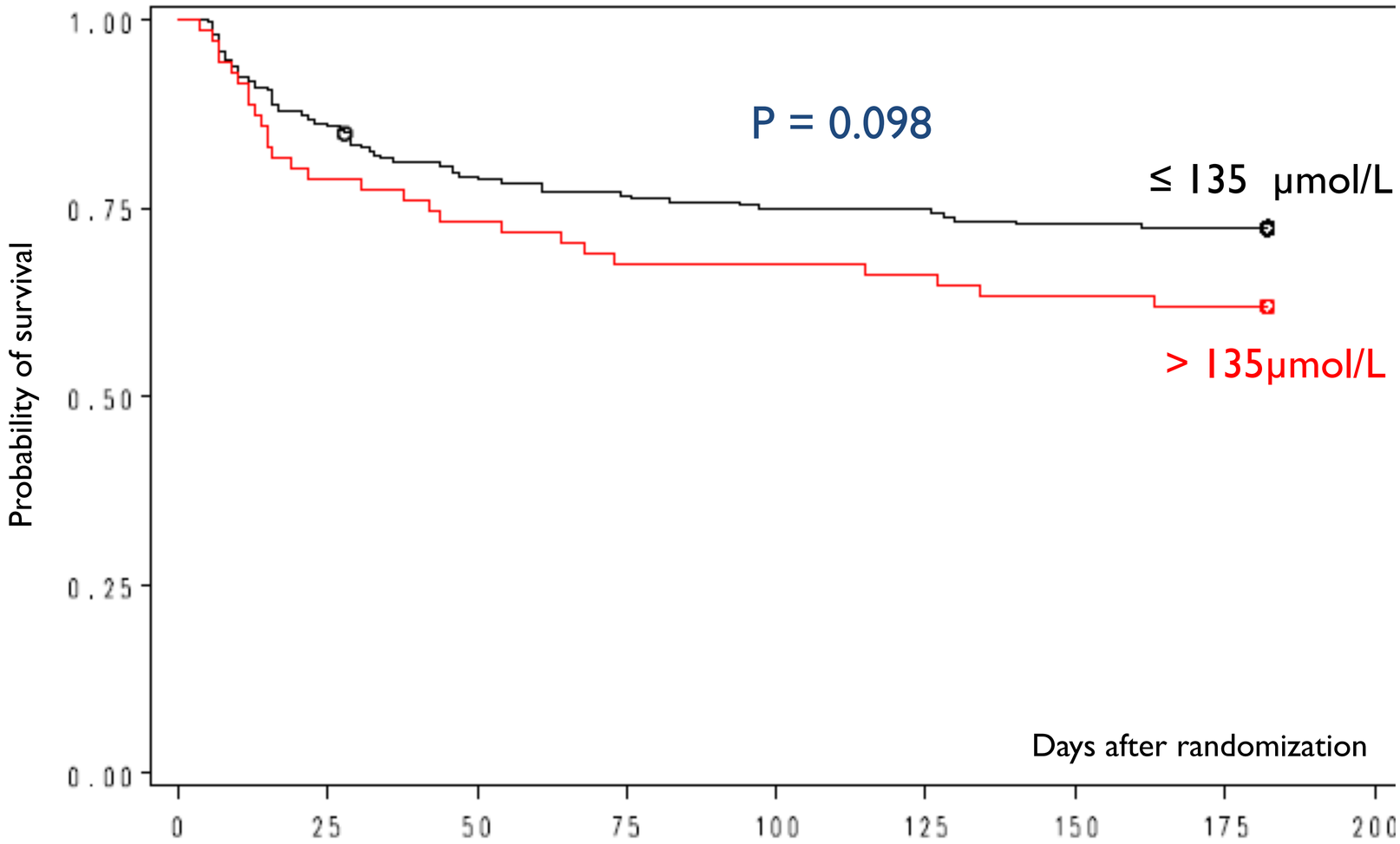


N=301

Van Zanten AR, with permission, MetaPlus unpublished data

Survival & Gln level increase

(day 4-baseline, cut-off 135µmol/L)



Van Zanten AR, with permission, MetaPlus unpublished data

Glutamine and antioxidants: status of their use in critical illness

Van Zanten AR. Curr Opin Clin Nutr Metab Care. 2015 Mar;18(2):179-86.

Issue 15
September 2014

NIBBLE

Nutrition Information Byte

Brought to you by www.criticalcarenutrition.com and your ICU Dietitian

Critical Care Nutrition

CRITICAL CARE NUTRITION ACADEMY

Consequences of the REDOXS and MetaPlus trials: the end of an era of glutamine and antioxidant supplementation for critically ill patients?

- There are now 2 studies (REDOXS & MetaPlus) that suggest that glutamine and antioxidants are harmful in critically ill patient populations.
- Evidence in support of glutamine and antioxidants comes from old, single-centered RCTs and individually are inconclusive.
- The positive signal is only observed in meta-analysis of these RCTs which has not been confirmed in recent, large-scale, multi-center trials.
- Given that our first dictum in medicine is to do no harm, we cannot be confident that supplemental glutamine and antioxidants are safe, whether provided enterally or parenterally, whether high or low dose.
- More research on the safety and efficacy of glutamine and antioxidants is needed before treatment recommendations can be considered.

van Zanten AR, Hofman Z, Heyland DK. JPEN J Parenter Enteral Nutr. 2015 Jan 7

van Zanten *et al. Critical Care* (2015) 19:294
DOI 10.1186/s13054-015-1002-x

CRITICAL CARE

RESEARCH Open Access

Enteral glutamine supplementation in critically ill patients: a systematic review and meta-analysis

Arthur R. H. van Zanten[1], Rupinder Dhaliwal[2], Dominique Garrel[3] and Daren K. Heyland[2*]

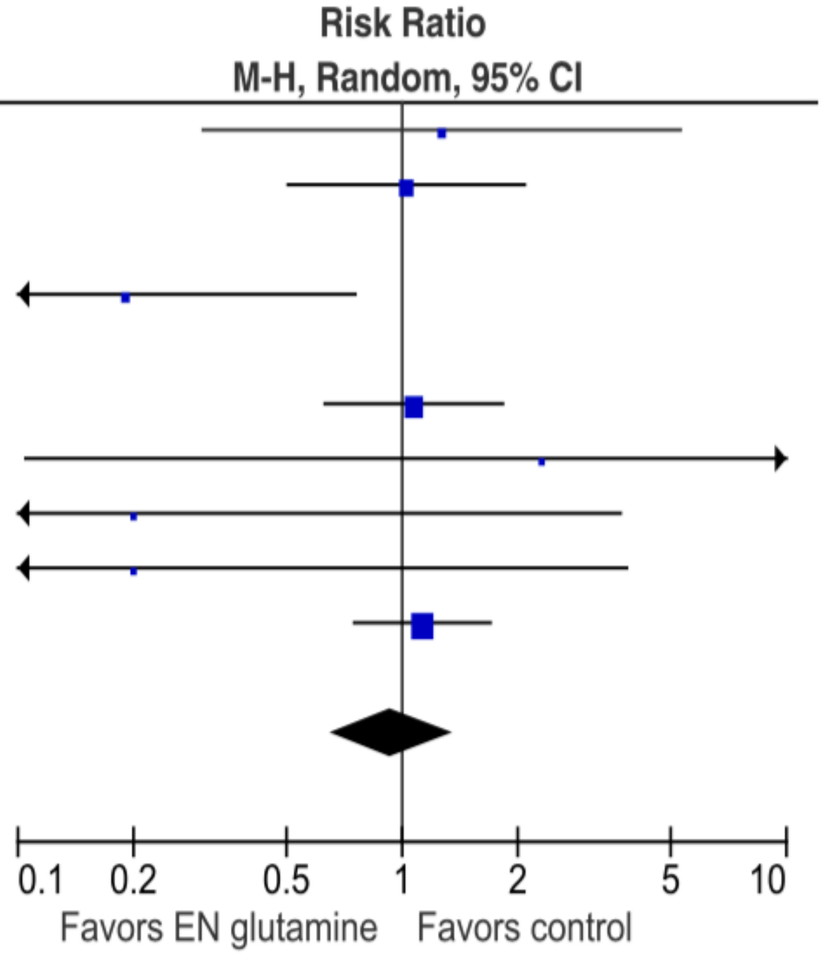
Meta-Analysis Enteral Glutamine

Hospital Mortality, all studies

Study or Subgroup	EN glutamine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Houdijk	4	41	3	39	6.1%	1.27 [0.30, 5.31]	1998
Jones	10	26	9	24	19.2%	1.03 [0.50, 2.08]	1999
Brantley	0	31	0	41		Not estimable	2000
Garrel	2	21	12	24	6.5%	0.19 [0.05, 0.76]	2003
Zhou	0	20	0	20		Not estimable	2003
Hall	24	179	23	184	27.6%	1.07 [0.63, 1.83]	2003
Lou	1	12	0	9	1.4%	2.31 [0.10, 50.85]	2007
McQuiggan	0	10	2	10	1.6%	0.20 [0.01, 3.70]	2008
Pattanshetti	0	15	2	15	1.5%	0.20 [0.01, 3.85]	2009
van Zanten	38	152	33	149	36.2%	1.13 [0.75, 1.70]	2014
Total (95% CI)		**507**		**515**	**100.0%**	**0.94 [0.65, 1.36]**	
Total events	79		84				

Heterogeneity: Tau² = 0.06; Chi² = 8.86, df = 7 (P = 0.26); I² = 21%

Test for overall effect: Z = 0.34 (P = 0.74)



van Zanten et al. Critical Care (2015) 19:294

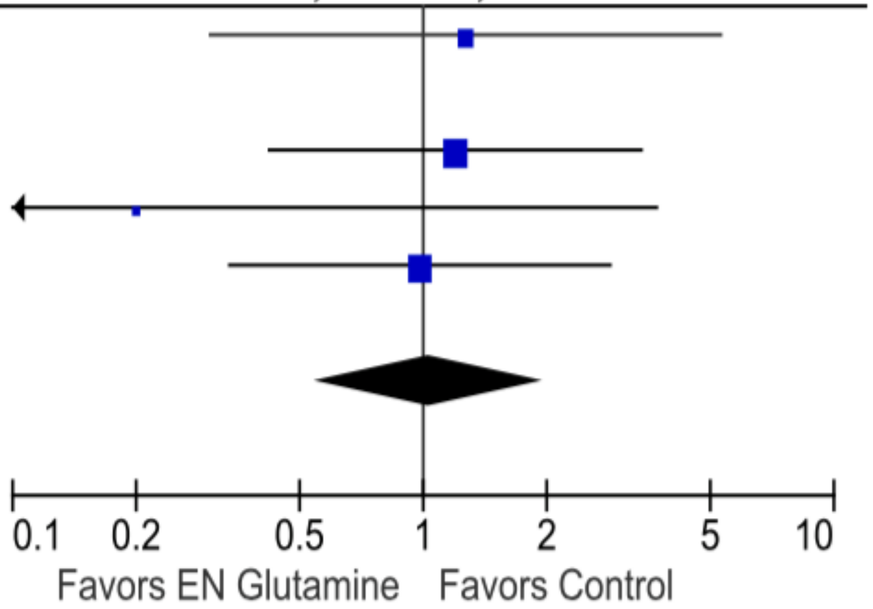
Meta-Analysis Enteral Glutamine

Hospital Mortality, trauma subgroup analysis

Study or Subgroup	EN Glutamine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Houdijk	4	41	3	39	20.3%	1.27 [0.30, 5.31]	1998
Brantley	0	31	0	41		Not estimable	2000
Hall	7	76	6	78	38.2%	1.20 [0.42, 3.40]	2003
McQuiggan	0	10	2	10	4.9%	0.20 [0.01, 3.70]	2008
van Zanten	6	55	6	54	36.5%	0.98 [0.34, 2.86]	2014
Total (95% CI)		**213**		**222**	**100.0%**	**1.03 [0.54, 1.97]**	
Total events	17		17				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.39$, df = 3 (P = 0.71); $I^2 = 0\%$

Test for overall effect: Z = 0.10 (P = 0.92)



van Zanten et al. Critical Care (2015) 19:294

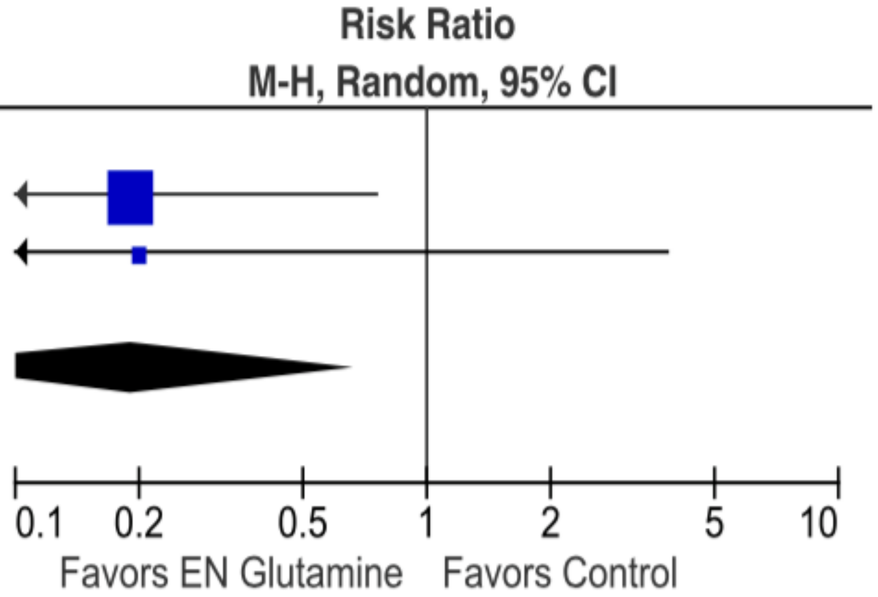
Meta-Analysis Enteral Glutamine

Hospital Mortality, burns subgroup analysis

Study or Subgroup	EN Glutamine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Zhou	0	20	0	20		Not estimable	2003
Garrel	2	21	12	24	82.2%	0.19 [0.05, 0.76]	2003
Pattanshetti	0	15	2	15	17.8%	0.20 [0.01, 3.85]	2009
Total (95% CI)		**56**		**59**	**100.0%**	**0.19 [0.06, 0.67]**	
Total events	2		14				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.00$, df = 1 (P = 0.98); $I^2 = 0\%$

Test for overall effect: Z = 2.59 (P = 0.010)



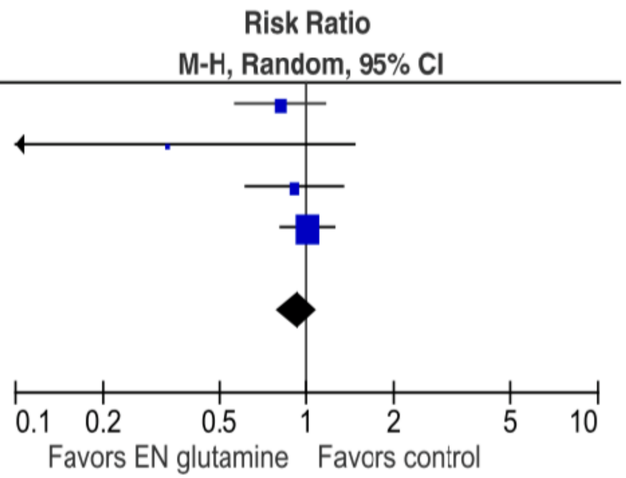
van Zanten et al. Critical Care (2015) 19:294

Meta-Analysis Enteral Glutamine

Infectious complications, all studies

Study or Subgroup	EN glutamine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Houdijk	20	35	26	37	21.5%	0.81 [0.57, 1.16]	1998
Zhou	2	20	6	20	1.2%	0.33 [0.08, 1.46]	2003
Hall	38	179	43	184	18.4%	0.91 [0.62, 1.33]	2003
van Zanten	80	152	78	149	58.8%	1.01 [0.81, 1.25]	2014
Total (95% CI)		**386**		**390**	**100.0%**	**0.93 [0.79, 1.10]**	
Total events	140		153				

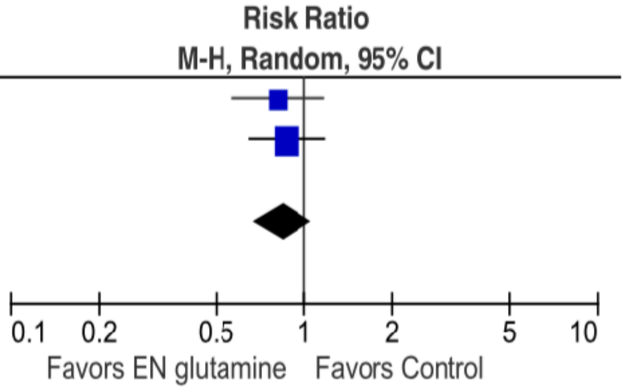
Heterogeneity: Tau² = 0.00; Chi² = 2.94, df = 3 (P = 0.40); I² = 0%
Test for overall effect: Z = 0.86 (P = 0.39)



Infectious complications, trauma subgroup analysis

Study or Subgroup	EN glutamine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Houdijk	20	35	26	37	40.5%	0.81 [0.57, 1.16]	1998
van Zanten	32	55	36	54	59.5%	0.87 [0.65, 1.17]	2014
Total (95% CI)		**90**		**91**	**100.0%**	**0.85 [0.68, 1.06]**	
Total events	52		62				

Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 1.43 (P = 0.15)



van Zanten et al. Critical Care (2015) 19:294

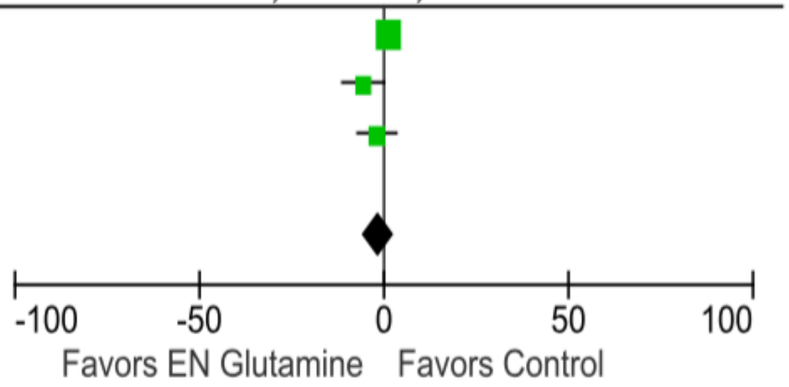
Meta-Analysis Enteral Glutamine

ICU LOS, all studies

Study or Subgroup	EN Glutamine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Lou	8.1	0.4	12	6.9	0.9	9	47.5%	1.20 [0.57, 1.83]	2007
McQuiggan	4.8	6.7	10	10.4	6.2	10	25.3%	-5.60 [-11.26, 0.06]	2008
van Zanten	23.7	22.4	152	25.6	24	149	27.1%	-1.90 [-7.15, 3.35]	2014
Total (95% CI)			**174**			**168**	**100.0%**	**-1.36 [-5.51, 2.78]**	

Heterogeneity: Tau² = 9.30; Chi² = 6.73, df = 2 (P = 0.03); I² = 70%

Test for overall effect: Z = 0.65 (P = 0.52)

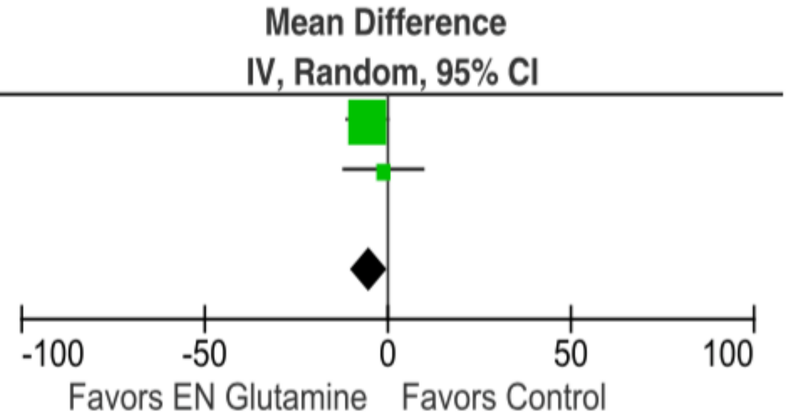


ICU LOS, trauma subgroup analysis

Study or Subgroup	EN Glutamine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
McQuiggan	4.8	6.7	10	10.4	6.2	10	78.6%	-5.60 [-11.26, 0.06]	2008
van Zanten	31.3	30.3	55	32.5	27.5	54	21.4%	-1.20 [-12.06, 9.66]	2014
Total (95% CI)			**65**			**64**	**100.0%**	**-4.66 [-9.68, 0.36]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 1 (P = 0.48); I² = 0%

Test for overall effect: Z = 1.82 (P = 0.07)



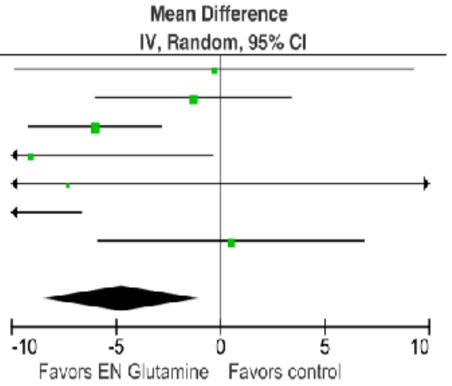
van Zanten et al. Critical Care (2015) 19:294

Meta-Analysis Enteral Glutamine

Hospital LOS, all studies

Study or Subgroup	Enteral Glutamine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Houdijk	32.7	17.1	35	33	23.8	37	10.7%	-0.30 [-9.83, 9.23]	1998
Brantley	19.5	8.8	31	20.8	11.5	41	21.7%	-1.30 [-5.99, 3.39]	2000
Zhou	67	4	20	73	6	20	26.3%	-6.00 [-9.16, -2.84]	2003
Peng	46.59	12.98	25	55.68	17.36	23	12.0%	-9.09 [-17.82, -0.36]	2004
McQuiggan	32	13.6	10	39.3	33.6	10	2.7%	-7.30 [-29.77, 15.17]	2008
Pattanshetti	22.73	9.13	15	39.73	18.27	15	9.6%	-17.00 [-27.34, -6.66]	2009
van Zanten	38.2	28.9	152	37.7	27.5	149	17.0%	0.50 [-5.87, 6.87]	2014
Total (95% CI)			**288**			**295**	**100.0%**	**-4.73 [-8.56, -0.90]**	

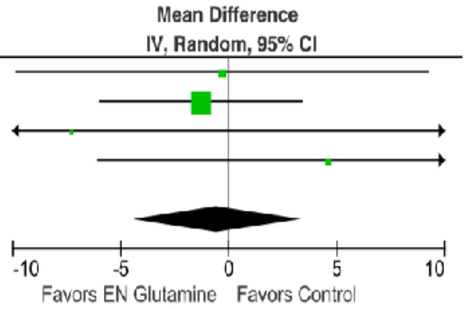
Heterogeneity: $Tau^2 = 11.91$; $Chi^2 = 12.50$, df = 6 (P = 0.05); $I^2 = 52\%$
Test for overall effect: Z = 2.42 (P = 0.02)



Hospital LOS, trauma subgroup analysis

Study or Subgroup	EN Glutamine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Houdijk	32.7	17.1	35	33	23.8	37	16.4%	-0.30 [-9.83, 9.23]	1998
Brantley	19.5	8.8	31	20.8	11.5	41	67.6%	-1.30 [-5.99, 3.39]	2000
McQuiggan	32	13.6	10	39.3	33.6	10	2.9%	-7.30 [-29.77, 15.17]	2008
van Zanten	44.4	31.2	55	39.8	25.3	54	13.1%	4.60 [-6.05, 15.25]	2014
Total (95% CI)			**131**			**142**	**100.0%**	**-0.54 [-4.40, 3.31]**	

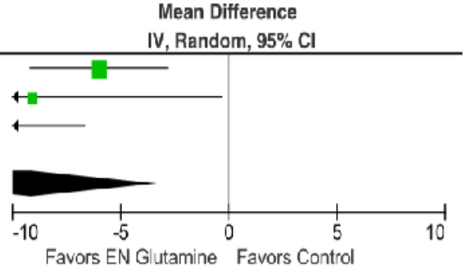
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.35$, df = 3 (P = 0.72); $I^2 = 0\%$
Test for overall effect: Z = 0.27 (P = 0.78)



Hospital LOS, burns subgroup analysis

Study or Subgroup	EN Glutamine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Zhou	67	4	20	73	6	20	52.4%	-6.00 [-9.16, -2.84]	2003
Peng	46.59	12.98	25	55.68	17.36	23	26.3%	-9.09 [-17.82, -0.36]	2004
Pattanshetti	22.73	9.13	15	39.73	18.27	15	21.3%	-17.00 [-27.34, -6.66]	2009
Total (95% CI)			**60**			**58**	**100.0%**	**-9.16 [-15.06, -3.26]**	

Heterogeneity: $Tau^2 = 14.70$; $Chi^2 = 4.19$, df = 2 (P = 0.12); $I^2 = 52\%$
Test for overall effect: Z = 3.04 (P = 0.002)



van Zanten et al. Critical Care (2015) 19:294

Meta-Analysis Enteral Glutamine

- Enteral GLN given in conjunction with EN support does not confer significant reductions in hospital mortality among critically ill patients, including trauma patients. However, it may reduce hospital mortality in burn patients.
- No effects on infectious morbidity or ICU LOS were observed.
- Hospital LOS was significantly reduced in critically ill and burn patients but not in trauma patients.
- However, the results of our meta-analysis are based mainly on smaller, single-center studies, and two recent multicenter trials have suggested potential harm of GLN.
- Therefore, enteral GLN supplementation cannot be recommended for critically ill patients.
- In burn patients, larger studies are warranted, as our observations of a beneficial effect are based on a small number of patients. Such a trial is currently underway worldwide (citation: see Clinical trials. gov ID #NCT00985205).

van Zanten et al. Critical Care (2015) 19:294

15 reasons to doubt the glutamine deficiency hypothesis

- Too simple concept
- Low plasma levels are inconsistent
- Sometimes high baseline levels
- No correlation disease severity
- Supplementation: no reduction endogenous production
- RCTs show harm
- High baseline glutamine associated with harm
- Conversion to citrulline and arginine
- No benefits in meta-analyses
- High-discharge glutamine associated with 1-year mortality
- Interaction with renal function
- Larger increase from baseline higher mortality
- Benefits only from older trials
- Benefits only from single center trials
- Low baseline associated with lower mortality

Van Zanten AR. Curr Opin Clin Nutr Metab Care. 2015 Mar;18(2):179-86.

In healthy elderly men whey protein is better absorbed and leads to greater muscle synthetic response

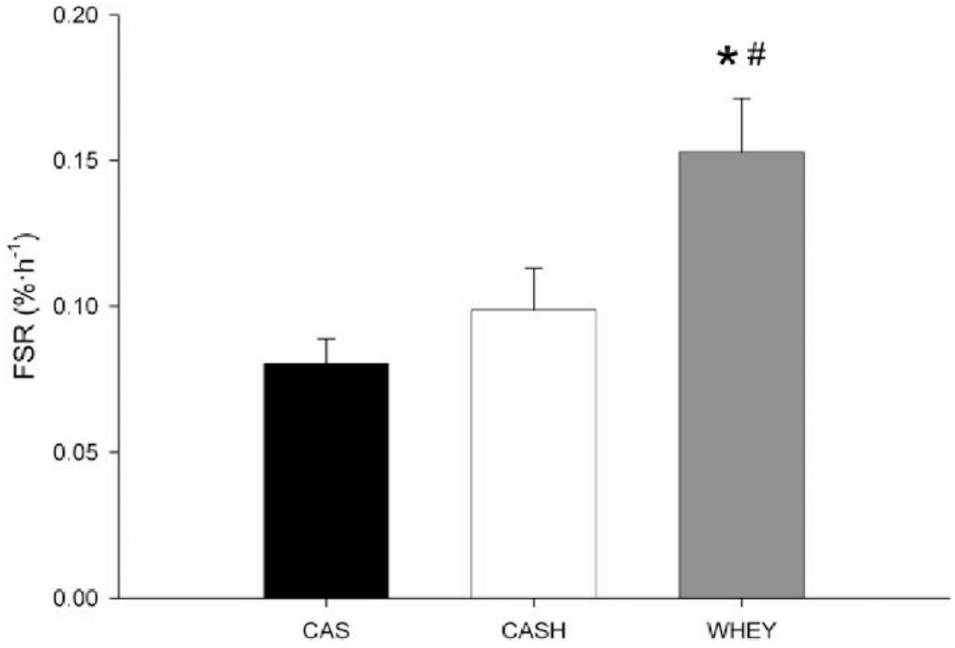
CRITICAL CARE NUTRITION ACADEMY

No ICU data

Amino acid composition of the proteins[1]

	Whey	Casein	Casein hydrolysate
Alanine (g)	1.0	0.6	0.6
Arginine (g)	0.5	0.7	0.7
Aspartic acid (g)	2.3	1.3	1.3
Cysteine (g)	0.7	0.1	0.1
Glutamic acid (g)	3.2	4.1	4.1
Glycine (g)	0.4	0.3	0.3
Histidine (g)	0.4	0.5	0.5
Isoleucine (g)	1.2	1.1	1.1
Leucine (g)	2.5	1.7	1.7
Lysine (g)	2.1	1.4	1.4
Methionine (g)	0.4	0.5	0.5
Phenylalanine (g)	0.7	0.9	0.9
Proline (g)	0.7	2.1	2.1
Serine (g)	0.7	1.3	1.3
Threonine (g)	0.9	0.8	0.8
Tryptophan (g)	0.5	0.2	0.2
Tyrosine (g)	0.8	1.1	1.1
Valine (g)	1.0	1.3	1.3
Total AA (g)	20.0	20.0	20.0
Total NEAA (g)	10.7	12.1	12.1
Total EAA (g)	9.3	7.9	7.9

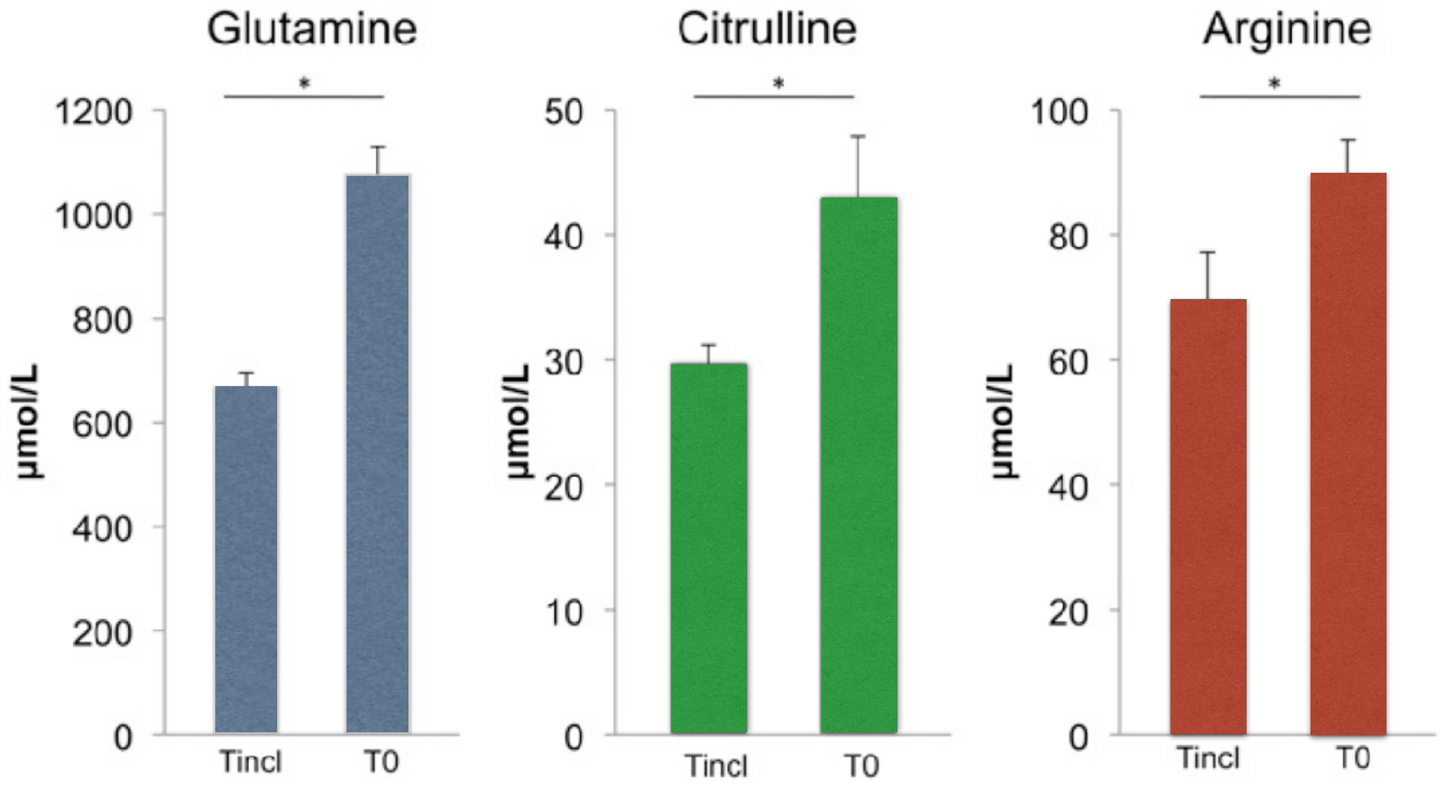
[1] Amounts are shown in g per 20 g protein. AA, amino acids; EAA, essential AA; NEAA, non-EAA.



Whey protein is more effective than casein and casein hydrolysate at promoting postprandial muscle protein accretion in healthy older men. The greater muscle protein synthetic response to whey ingestion is likely attributable to both its faster digestion and absorption kinetics and higher leucine content, which thereby further increases the postprandial rise in plasma leucine concentrations.

Pennings, Van Loon et al. Am J Clin Nutr 2011;93:997–1005

Non-controlled side effects

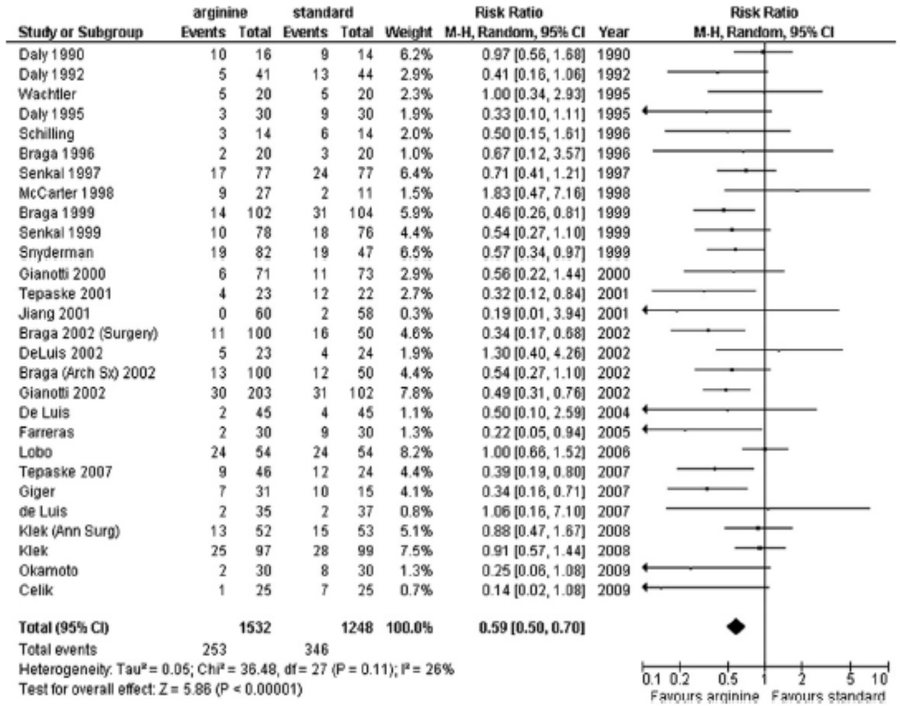


Mean (SEM) plasma concentrations of glutamine, citrulline, and arginine at TIncl and after the administration of intravenous 0.5 g alanyl-glutamine/kg per day just before T0 (n = 7). Student's t test was used to determine significant differences in amino acid concentrations between TIncl and T0. *P , 0.05. TIncl, time of inclusion; T0, start of the tracer infusion.

Buijs N et al. Am J Clin Nutr 2014;100:1385–91.

Timing and arginine

Pre/Peri-operatively
Reduction in infections p <0.0001

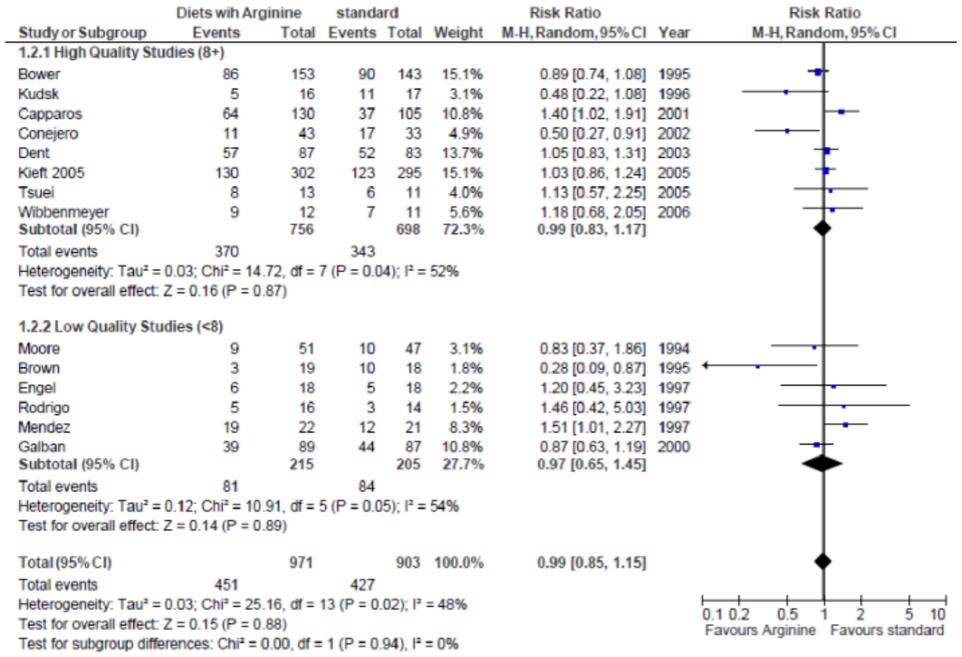


Study or Subgroup	arginine Events	Total	standard Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Daly 1990	10	16	9	14	6.2%	0.97 [0.56, 1.68]	1990
Daly 1992	5	41	13	44	2.9%	0.41 [0.16, 1.06]	1992
Wachtler	5	20	5	20	2.3%	1.00 [0.34, 2.93]	1995
Daly 1995	3	30	9	30	1.9%	0.33 [0.10, 1.11]	1995
Schilling	3	14	6	14	2.0%	0.50 [0.15, 1.61]	1996
Braga 1996	2	20	3	20	1.0%	0.67 [0.12, 3.57]	1996
Senkal 1997	17	77	24	77	6.4%	0.71 [0.41, 1.21]	1997
McCarter 1998	9	27	2	11	1.5%	1.83 [0.47, 7.16]	1998
Braga 1999	14	102	31	104	5.9%	0.46 [0.26, 0.81]	1999
Senkal 1999	10	78	18	76	4.4%	0.54 [0.27, 1.10]	1999
Snyderman	19	82	19	47	6.5%	0.57 [0.34, 0.97]	1999
Gianotti 2000	6	71	11	73	2.9%	0.56 [0.22, 1.44]	2000
Tepaske 2001	4	23	12	22	2.7%	0.32 [0.12, 0.84]	2001
Jiang 2001	0	60	2	58	0.3%	0.19 [0.01, 3.94]	2001
Braga 2002 (Surgery)	11	100	16	50	4.6%	0.34 [0.17, 0.68]	2002
DeLuis 2002	5	23	4	24	1.9%	1.30 [0.40, 4.26]	2002
Braga (Arch Sx) 2002	13	100	12	50	4.4%	0.54 [0.27, 1.10]	2002
Gianotti 2002	30	203	31	102	7.8%	0.49 [0.31, 0.76]	2002
De Luis	2	45	4	45	1.1%	0.50 [0.10, 2.59]	2004
Farreras	2	30	9	30	1.3%	0.22 [0.05, 0.94]	2005
Lobo	24	54	24	54	8.2%	1.00 [0.66, 1.52]	2006
Tepaske 2007	9	46	12	24	4.4%	0.39 [0.19, 0.80]	2007
Giger	7	31	10	15	4.1%	0.34 [0.16, 0.71]	2007
de Luis	2	35	2	37	0.8%	1.06 [0.16, 7.10]	2007
Klek (Ann Surg)	13	52	15	53	5.1%	0.88 [0.47, 1.67]	2008
Klek	25	97	28	99	7.5%	0.91 [0.57, 1.44]	2008
Okamoto	2	30	8	30	1.3%	0.25 [0.06, 1.08]	2009
Celik	1	25	7	25	0.7%	0.14 [0.02, 1.08]	2009
Total (95% CI)		**1532**		**1248**	**100.0%**	**0.59 [0.50, 0.70]**	
Total events	253		346				

Heterogeneity: Tau² = 0.05; Chi² = 36.48, df = 27 (P = 0.11); I² = 26%
Test for overall effect: Z = 5.86 (P < 0.00001)

Risk Ratio M-H, Random, 95% CI
0.1 0.2 0.5 1 2 5 10
Favours arginine Favours standard

ICU
No reduction in infections p =0.88



Study or Subgroup	Diets wih Arginine Events	Total	standard Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.2.1 High Quality Studies (8+)							
Bower	86	153	90	143	15.1%	0.89 [0.74, 1.08]	1995
Kudsk	5	16	11	17	3.1%	0.48 [0.22, 1.08]	1996
Capparos	64	130	37	105	10.8%	1.40 [1.02, 1.91]	2001
Conejero	11	43	17	33	4.9%	0.50 [0.27, 0.91]	2002
Dent	57	87	52	83	13.7%	1.05 [0.83, 1.31]	2003
Kieft 2005	130	302	123	295	15.1%	1.03 [0.86, 1.24]	2005
Tsuei	8	13	6	11	4.0%	1.13 [0.57, 2.25]	2005
Wibbenmeyer	9	12	7	11	5.6%	1.18 [0.68, 2.05]	2006
Subtotal (95% CI)		756		698	72.3%	0.99 [0.83, 1.17]	
Total events	370		343				

Heterogeneity: Tau² = 0.03; Chi² = 14.72, df = 7 (P = 0.04); I² = 52%
Test for overall effect: Z = 0.16 (P = 0.87)

1.2.2 Low Quality Studies (<8)							
Moore	9	51	10	47	3.1%	0.83 [0.37, 1.86]	1994
Brown	3	19	10	18	1.8%	0.28 [0.09, 0.87]	1995
Engel	6	18	5	18	2.2%	1.20 [0.45, 3.23]	1997
Rodrigo	5	16	3	14	1.5%	1.46 [0.42, 5.03]	1997
Mendez	19	22	12	21	8.3%	1.51 [1.01, 2.27]	1997
Galban	39	89	44	87	10.8%	0.87 [0.63, 1.19]	2000
Subtotal (95% CI)		215		205	27.7%	0.97 [0.65, 1.45]	
Total events	81		84				

Heterogeneity: Tau² = 0.12; Chi² = 10.91, df = 5 (P = 0.05); I² = 54%
Test for overall effect: Z = 0.14 (P = 0.89)

Total (95% CI)		971		903	100.0%	0.99 [0.85, 1.15]	
Total events	451		427				

Heterogeneity: Tau² = 0.03; Chi² = 25.16, df = 13 (P = 0.02); I² = 48%
Test for overall effect: Z = 0.15 (P = 0.88)
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.94), I² = 0%

Risk Ratio M-H, Random, 95% CI
0.1 0.2 0.5 1 2 5 10
Favours Arginine Favours standard

CCPG 2016. www.criticalcarenutrition.com
Drover JW et al. Am Coll Surg. 2011;212(3):385-99

Clinical Nutrition 35 (2016) 18–26

Contents lists available at ScienceDirect

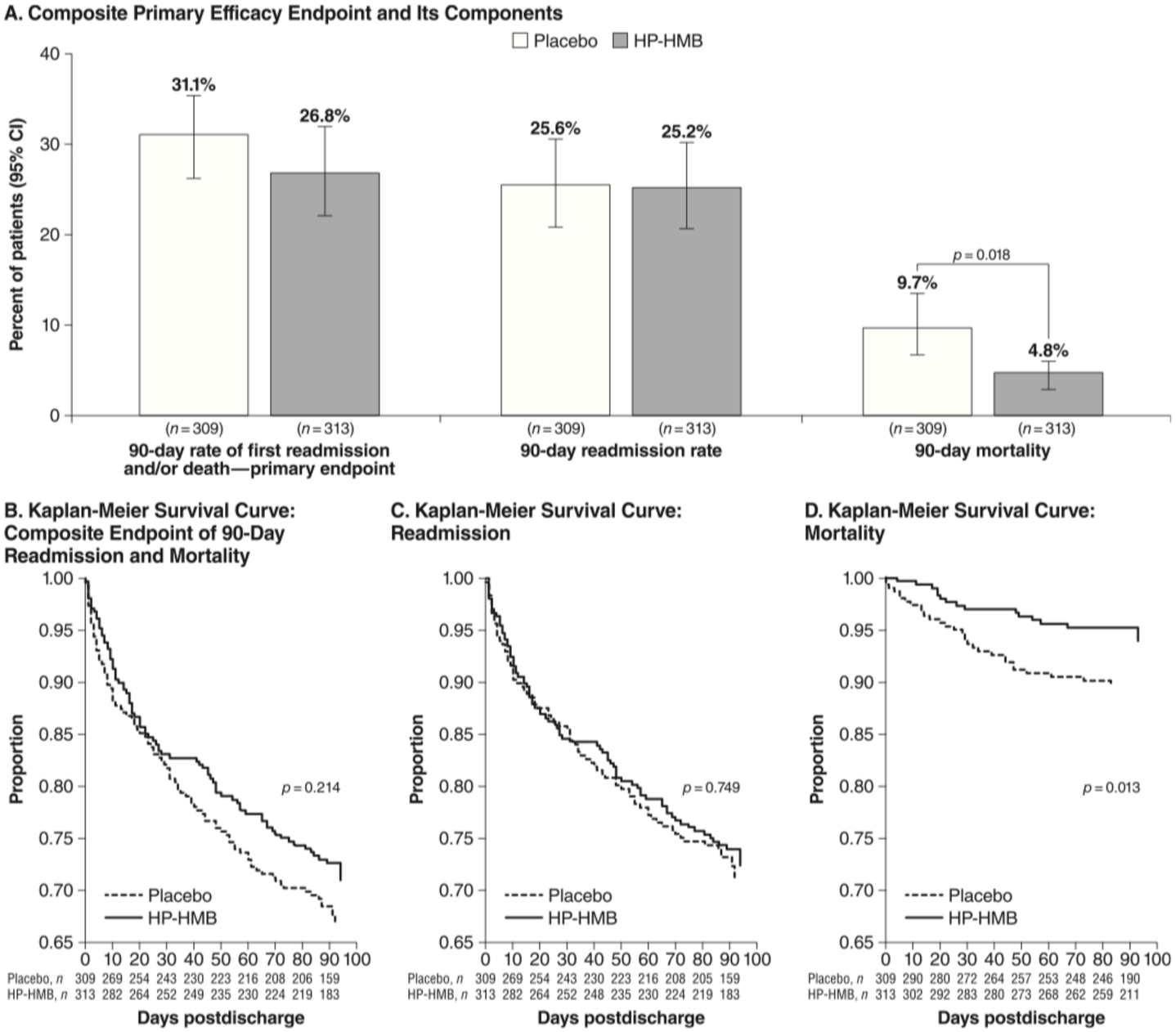
Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Randomized control trials

Readmission and mortality in malnourished, older, hospitalized adults treated with a specialized oral nutritional supplement: A randomized clinical trial

Nicolaas E. Deutz [a, *], Eric M. Matheson [b], Laura E. Matarese [c], Menghua Luo [d], Geraldine E. Baggs [d], Jeffrey L. Nelson [d], Refaat A. Hegazi [d], Kelly A. Tappenden [e], Thomas R. Ziegler [f], on behalf of the NOURISH Study Group



Nourish Study

ONS: RCT 1:1

Randomization to:

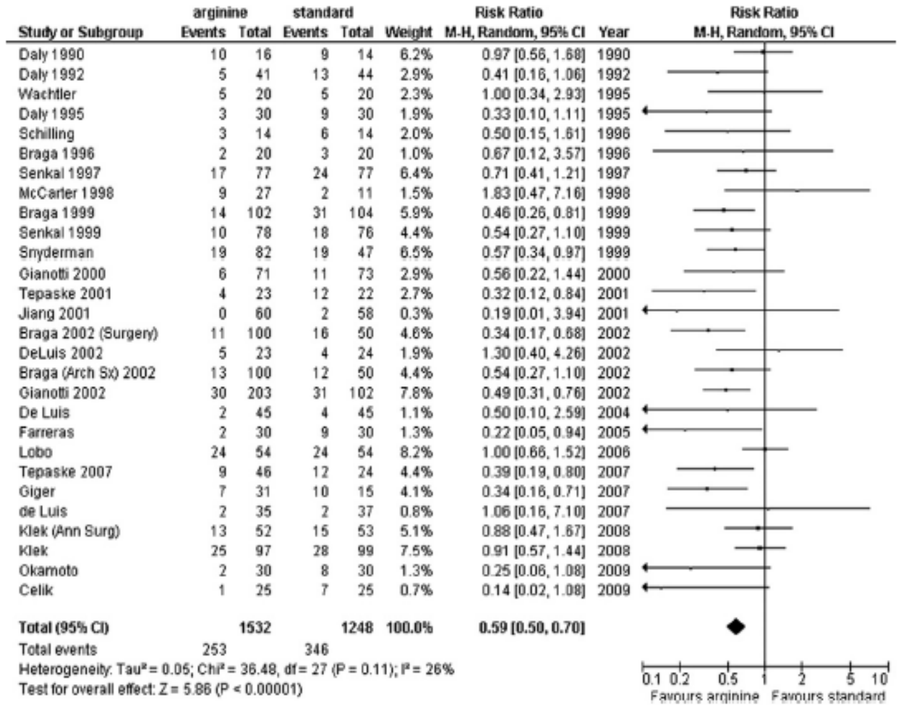
HP-HMB nutrient-dense ready-to-drink liquid with 350 kcal, 20 g protein, 11 g fat, 44 g carbohydrate, 1.5 g calcium-HMB, 160 IU vitamin D and other essential micronutrients.

The placebo, also a ready-to drink liquid contained 48 kcal, 12 g carbohydrate, and 10 mg vitamin C, but no other macro- or micronutrients.

Deutz NE, et al. Clinical Nutrition 35 (2016) 18-26

Timing and arginine

Pre/Peri-operatively
Reduction in infections p <0.0001

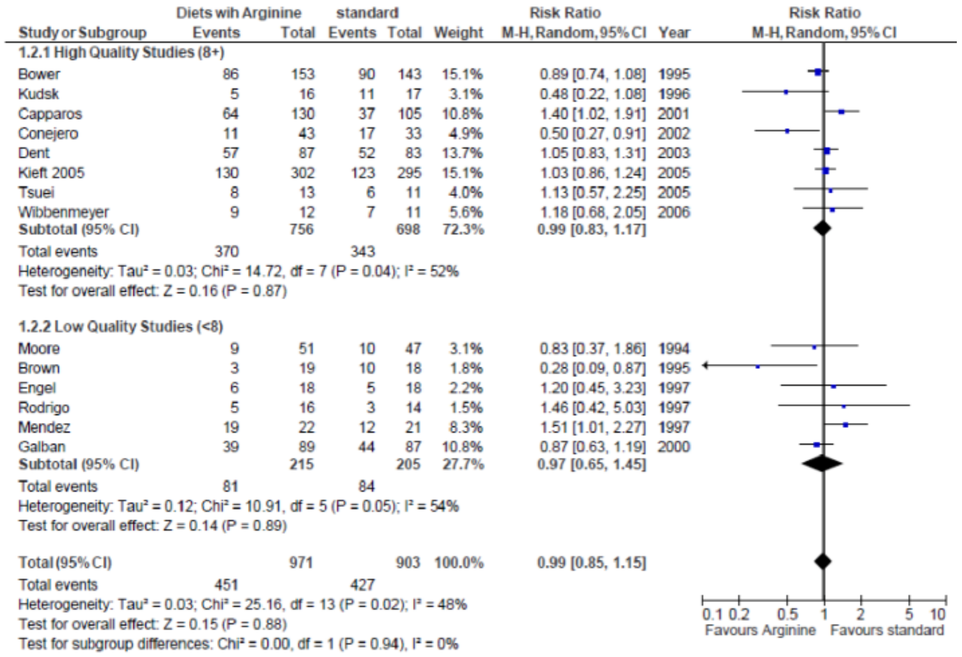


Study or Subgroup	arginine Events	Total	standard Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Daly 1990	10	16	9	14	6.2%	0.97 [0.56, 1.68]	1990
Daly 1992	5	41	13	44	2.9%	0.41 [0.16, 1.06]	1992
Wachtler	5	20	5	20	2.3%	1.00 [0.34, 2.93]	1995
Daly 1995	3	30	9	30	1.9%	0.33 [0.10, 1.11]	1995
Schilling	3	14	6	14	2.0%	0.50 [0.15, 1.61]	1996
Braga 1996	2	20	3	20	1.0%	0.67 [0.12, 3.57]	1996
Senkal 1997	17	77	24	77	6.4%	0.71 [0.41, 1.21]	1997
McCarter 1998	9	27	2	11	1.5%	1.83 [0.47, 7.16]	1998
Braga 1999	14	102	31	104	5.9%	0.46 [0.26, 0.81]	1999
Senkal 1999	10	78	18	76	4.4%	0.54 [0.27, 1.10]	1999
Snyderman	19	82	19	47	6.5%	0.57 [0.34, 0.97]	1999
Gianotti 2000	6	71	11	73	2.9%	0.56 [0.22, 1.44]	2000
Tepaske 2001	4	23	12	22	2.7%	0.32 [0.12, 0.84]	2001
Jiang 2001	0	60	2	58	0.3%	0.19 [0.01, 3.94]	2001
Braga 2002 (Surgery)	11	100	16	50	4.6%	0.34 [0.17, 0.68]	2002
DeLuis 2002	5	23	4	24	1.9%	1.30 [0.40, 4.26]	2002
Braga (Arch Sx) 2002	13	100	12	50	4.4%	0.54 [0.27, 1.10]	2002
Gianotti 2002	30	203	31	102	7.8%	0.49 [0.31, 0.76]	2002
De Luis	2	45	4	45	1.1%	0.50 [0.10, 2.59]	2004
Farreras	2	30	9	30	1.3%	0.22 [0.05, 0.94]	2005
Lobo	24	54	24	54	8.2%	1.00 [0.66, 1.52]	2006
Tepaske 2007	9	46	12	24	4.4%	0.39 [0.19, 0.80]	2007
Giger	7	31	10	15	4.1%	0.34 [0.16, 0.71]	2007
de Luis	2	35	2	37	0.8%	1.06 [0.16, 7.10]	2007
Klek (Ann Surg)	13	52	15	53	5.1%	0.88 [0.47, 1.67]	2008
Klek	25	97	28	99	7.5%	0.91 [0.57, 1.44]	2008
Okamoto	2	30	8	30	1.3%	0.25 [0.06, 1.08]	2009
Celik	1	25	7	25	0.7%	0.14 [0.02, 1.08]	2009
Total (95% CI)		**1532**		**1248**	**100.0%**	**0.59 [0.50, 0.70]**	
Total events	253		346				

Heterogeneity: Tau² = 0.05; Chi² = 36.48, df = 27 (P = 0.11); I² = 26%
Test for overall effect: Z = 5.86 (P < 0.00001)

Risk Ratio M-H, Random, 95% CI
0.1 0.2 0.5 1 2 5 10
Favours arginine Favours standard

ICU
No reduction in infections p =0.88



Study or Subgroup	Diets wih Arginine Events	Total	standard Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.2.1 High Quality Studies (8+)							
Bower	86	153	90	143	15.1%	0.89 [0.74, 1.08]	1995
Kudsk	5	16	11	17	3.1%	0.48 [0.22, 1.08]	1996
Capparos	64	130	37	105	10.8%	1.40 [1.02, 1.91]	2001
Conejero	11	43	17	33	4.9%	0.50 [0.27, 0.91]	2002
Dent	57	87	52	83	13.7%	1.05 [0.83, 1.31]	2003
Kieft 2005	130	302	123	295	15.1%	1.03 [0.86, 1.24]	2005
Tsuei	8	13	6	11	4.0%	1.13 [0.57, 2.25]	2005
Wibbenmeyer	9	12	7	11	5.6%	1.18 [0.68, 2.05]	2006
Subtotal (95% CI)		756		698	72.3%	0.99 [0.83, 1.17]	
Total events	370		343				
Heterogeneity: Tau² = 0.03; Chi² = 14.72, df = 7 (P = 0.04); I² = 52%							
Test for overall effect: Z = 0.16 (P = 0.87)							
1.2.2 Low Quality Studies (<8)							
Moore	9	51	10	47	3.1%	0.83 [0.37, 1.86]	1994
Brown	3	19	10	18	1.8%	0.28 [0.09, 0.87]	1995
Engel	6	18	5	18	2.2%	1.20 [0.45, 3.23]	1997
Rodrigo	5	16	3	14	1.5%	1.46 [0.42, 5.03]	1997
Mendez	19	22	12	21	8.3%	1.51 [1.01, 2.27]	1997
Galban	39	89	44	87	10.8%	0.87 [0.63, 1.19]	2000
Subtotal (95% CI)		215		205	27.7%	0.97 [0.65, 1.45]	
Total events	81		84				
Heterogeneity: Tau² = 0.12; Chi² = 10.91, df = 5 (P = 0.05); I² = 54%							
Test for overall effect: Z = 0.14 (P = 0.89)							
Total (95% CI)		971		903	100.0%	0.99 [0.85, 1.15]	
Total events	451		427				
Heterogeneity: Tau² = 0.03; Chi² = 25.16, df = 13 (P = 0.02); I² = 48%							
Test for overall effect: Z = 0.15 (P = 0.88)							
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.94), I² = 0%							

Risk Ratio M-H, Random, 95% CI
0.1 0.2 0.5 1 2 5 10
Favours Arginine Favours standard

Drover JW et al. Am Coll Surg. 2011;212(3):385-99
CCPG 2016 www.criticalcarenutrition.com 2016

Timing and arginine

- **CCPG 2015 Recommendation: Based on 5 level 1 studies and 22 level 2 studies, we do not recommend diets supplemented with arginine and other select nutrients be used for critically ill patients.**
- **Given the possible harm in septic patients (Bower, Ross, Bertolini) and the increased costs, the committee decided to recommend against their use in critically ill patients.**

Arginine ↔ Citrulline + NO

Do not use arginine in septic ICU patients

Drover JW et al. Am Coll Surg. 2011;212(3):385-99
www.criticalcarenutrition.com 2016

My suggestions

- Enteral glutamine supplementation is not indicated, and in normal EN around 6 grams of glutamine per liter is available
- In PN consider to make a balanced AA solution as in normal PN no glutamine is available
- Do not go over recommended low dosages to do this, or consider to measure plasma glutamine levels

ESPEN ICU guidelines 2018

- **Recommendation 26: In patients with burns > 20% body surface area, additional enteral doses of GLN (0.3-0.5 g/kg/d) should be administered for 10-15 days as soon as EN is commenced.**
- **Grade of recommendation: B – strong consensus (95 % agreement)**
- **Recommendation 27: In critically ill trauma, additional EN doses of GLN (0.2-0.3 g/kg/d) can be administered for the first five days with EN. In case of complicated wound healing it can be administered for a longer period of ten to 15 days.**
- **Grade of recommendation: 0 – strong consensus (91 % agreement).**
- **Recommendation 28: In ICU patients except burn and trauma patients, additional enteral GLN should not be administered.**
- **Grade of recommendation: B – strong consensus (92.31 % agreement)**
- **Recommendation 29: In unstable and complex ICU patients, particularly in those suffering from liver and renal failure, parenteral GLN -dipeptide shall not be administered.**
- **Grade of recommendation: A – strong consensus (92.31 % agreement)**