ORIGINAL ARTICLE

Intravenous Vitamin C in Adults with Sepsis in the Intensive Care Unit

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Journal Club

24-oktober 2022

Linda van Wagenberg

Rationale & Hypothese

- Sepsis geeft oxidatieve stress
- Vitamine C remt weefsel schade door oxidatieve stress af

- Ascorbinezuur nodig voor het maken van cathecolamines
- Laag aanwezig in kritiek zieke patienten
- Mensen maken geen Vitamine C aan > Suppletie?

- 2017 Marik et al. Chest: combinatie van vitamine C, hydrocortison en thiamine bij sepsis
  - Mortaliteit treatment 8,5% vs 40,4% non-treatment
  - Single center

    - >> Lobby in vitamine C op ICUs

Vitamin C
IN SEPSIS

First10EM

Hypothese

- Lessening Organ Dysfunction with Vitamin C (LOVIT) trial
- A high dose of vitamin C would reduce the risk of death or persistent organ dysfunction at 28 days in adults with sepsis who were receiving vasopressor therapy in the intensive care unit (ICU)

Materiaal en Methoden

Design

- RCT
- Ratio 1:1 vitamin C vs. placebo
- Geblindeerd (1x apotheker niet geblindeerd)

Setting

- 35 volwassen ICUs in Canada, Frankrijk en Nieuw Zeeland. Volwassenen!

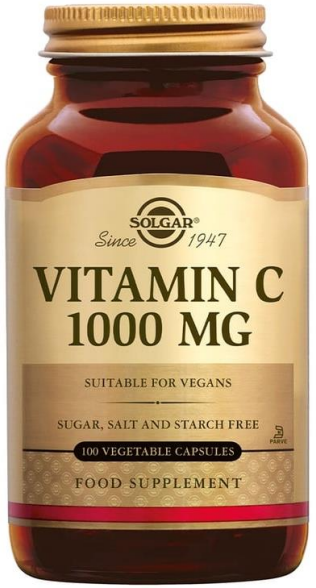
Inclusie

- Patiënten >18 jaar in ICU met verdenking/ bewezen infectie, opname <24 uur én vasopressie
- Exclusie bij contra-indicatie Vitamine C, gebruik vitamine C thuis, verwacht overlijden< 48h.

Materiaal en Methoden

<u>Interventie</u>

- Vitamine C 50mg/kg in 50ml opgelost vs placebo.
- Dosis 4d gedurende 96 uur, zo lang patiënt in ICU was.



Rekensom:
Volwassene 70kg> per dag 200mg/kg = 14 gram/ dag
Normale suppletie 1 gram/ dag

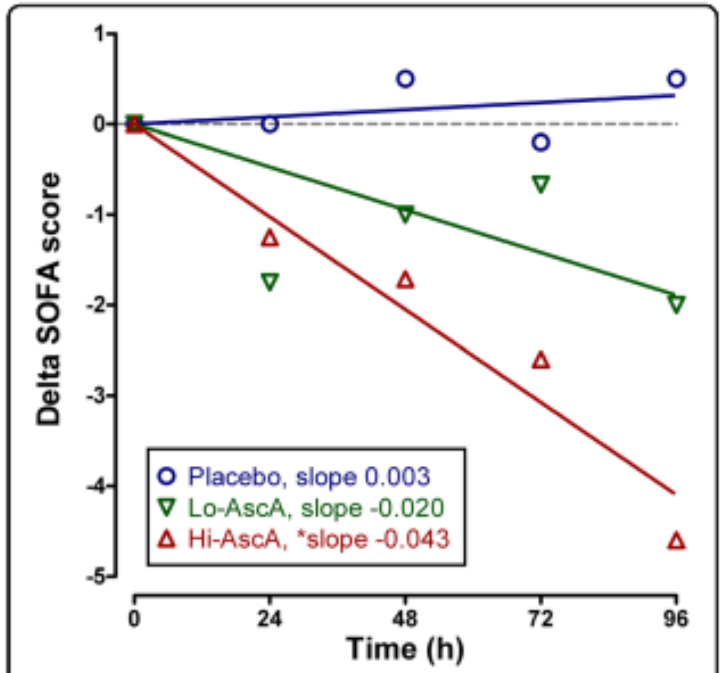


Figure 2 Effect of ascorbic acid infusion on Sequential Organ Failure Assessment (SOFA) score (days 0–4). Daily mean SOFA scores decreased over time with both doses of ascorbic acid infusion ($p < 0.05$ significantly non-zero) with the higher dose significantly less than placebo (Hi-AscA vs. placebo $p < 0.01$). Placebo (O), Lo-AscA (▼), Hi-AscA (▲).

Fowler et al. Journal of Translational Medicine 2014, 12:32
Low: vit C 50mg/kg/dag
High: vit C 200mg/kg/dag

Materiaal en Methoden

<u>Uitkomsten</u>

- Primair:
  - Mortaliteit dag 28 +
  - Persisterend orgaan falen (vasopressie, mechanische ventilatie, nieuw RRT) op dag 28

- Secundair:
  - Dagen zonder orgaandysfunctie (tot dag 28)
  - Mortaliteit tussen dag 28 en 6 maanden
  - QoL 6 maanden
  - Orgaan falen op dag 2,3,4,7,10, 14 en 28 (SOFA-score)
  - Biomarkers (lactaat, IL-1B, TNF-a, thrombomoduline, angiopoietin-2) op dag 3 en 7

- Safety outcomes
  - AKI stage 3, acute hemolyse, hypoglycemie

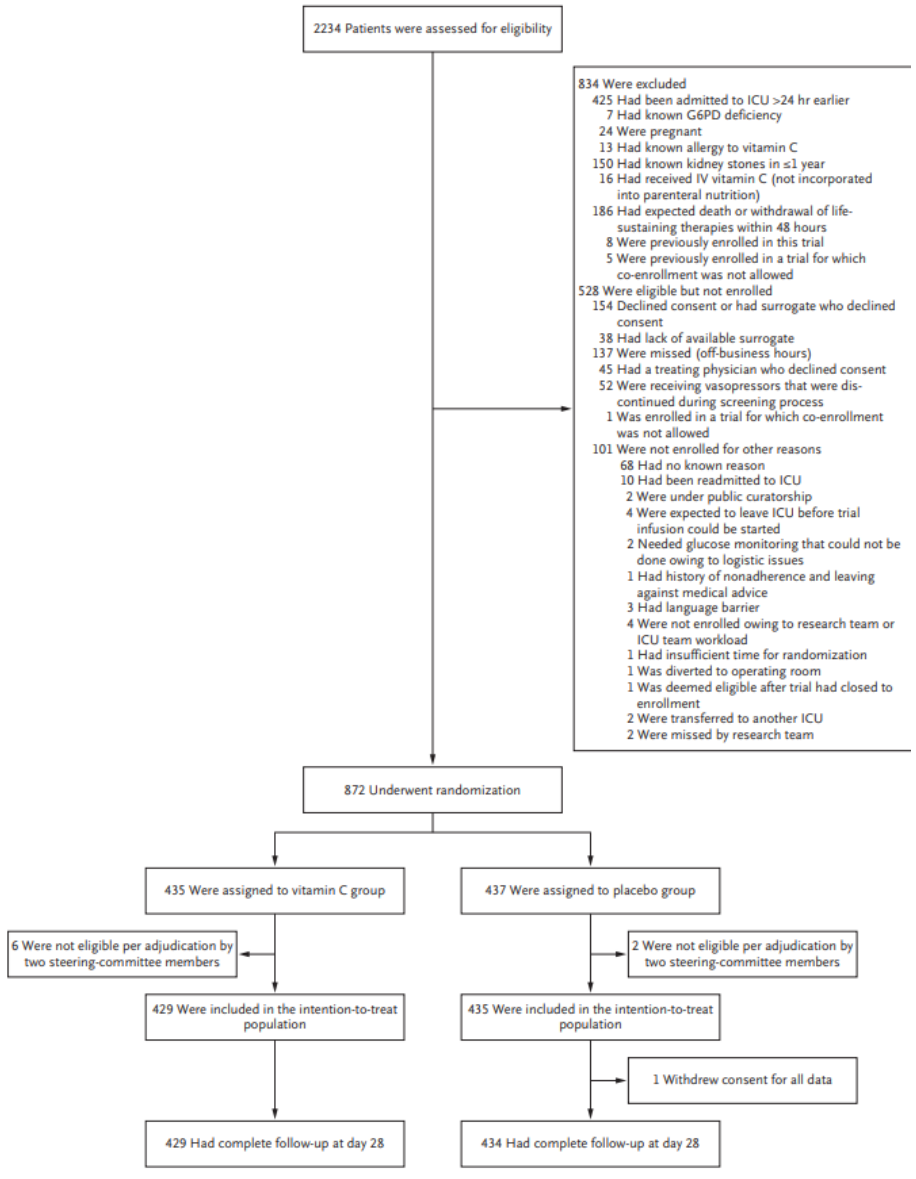
Materiaal en Methoden

<u>Sample size berekening</u>

- Verwachte mortaliteit en orgaandysfunctie op dag 28= 50%
- Aan te tonen verschil in mortaliteit 10% (power 80%)
  - Absolute risicoreductie in vitamine C groep 10%
  - Relatieve risicoreductie 20%
- Minimale groep 385 patiënten > gekozen voor n=400
- April 2020> Ook COVID+ patienten; Sample size vergroot

- Intention-to-treat analyse om superioriteit vitamine C aan te tonen

Uitkomsten –


2234 Patients were assessed for eligibility
834 Were excluded
425 Had been admitted to ICU >24 hr earlier
7 Had known G6PD deficiency
24 Were pregnant
13 Had known allergy to vitamin C
150 Had known kidney stones in ≤1 year
16 Had received IV vitamin C (not incorporated into parenteral nutrition)
186 Had expected death or withdrawal of life-sustaining therapies within 48 hours
8 Were previously enrolled in this trial
5 Were previously enrolled in a trial for which co-enrollment was not allowed
528 Were eligible but not enrolled
154 Declined consent or had surrogate who declined consent
38 Had lack of available surrogate
137 Were missed (off-business hours)
45 Had a treating physician who declined consent
52 Were receiving vasopressors that were dis-continued during screening process
1 Was enrolled in a trial for which co-enrollment was not allowed
101 Were not enrolled for other reasons
68 Had no known reason
10 Had been readmitted to ICU
2 Were under public curatorship
4 Were expected to leave ICU before trial infusion could be started
2 Needed glucose monitoring that could not be done owing to logistic issues
1 Had history of nonadherence and leaving against medical advice
3 Had language barrier
4 Were not enrolled owing to research team or ICU team workload
1 Had insufficient time for randomization
1 Was diverted to operating room
1 Was deemed eligible after trial had closed to enrollment
2 Were transferred to another ICU
2 Were missed by research team
872 Underwent randomization
435 Were assigned to vitamin C group
437 Were assigned to placebo group
6 Were not eligible per adjudication by two steering-committee members
2 Were not eligible per adjudication by two steering-committee members
429 Were included in the intention-to-treat population
435 Were included in the intention-to-treat population
1 Withdrew consent for all data
429 Had complete follow-up at day 28
434 Had complete follow-up at day 28

Uitkomsten - karakteristieken

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Vitamin C (N=429)	Placebo (N=433)†
Age — yr	65.0±14.0	65.2±13.8
Female sex — no. (%)	151 (35.2)	173 (40.0)
Admission type — no. (%)‡		
Medical	350 (81.6)	369 (85.2)
Emergency surgery	69 (16.1)	59 (13.6)
Elective surgery	10 (2.3)	5 (1.2)
APACHE II score§	24.2±7.4	24.1±7.9
SOFA score¶	10.2±3.4	10.1±3.7
Score on Clinical Frailty Scale‖	3.8±1.4	3.9±1.4
1 to 4 — no. (%)	312 (72.7)	308 (71.3)
≥5 — no. (%)	117 (27.3)	124 (28.7)
Primary site of infection — no. (%)**		
Pulmonary	145 (33.8)	159 (36.7)
Gastrointestinal or intra-abdominal	133 (31.0)	112 (25.9)
Blood	55 (12.8)	59 (13.6)
Skin or soft tissue	55 (12.8)	62 (14.3)
Urinary	49 (11.4)	55 (12.7)
Central nervous system	2 (0.5)	4 (0.9)
Other	30 (7.0)	27 (6.2)
SARS-CoV-2 positive — no. (%)††	37 (8.6)	26 (6.0)
Lactate — mmol/liter‡‡	3.4±3.2	3.0±2.8
Vitamin C — μmol/liter§§	20.6±70.6	19.1±39.7
Septic shock definition met — no./total no. (%)¶¶	195/327 (59.6)	183/326 (56.1)
Time from ICU admission to randomization — hr	12.9±8.2	12.3±6.7
Treatment — no. (%)		
Glucocorticoid‖‖	199 (46.4)	196 (45.4)
Mechanical ventilation	294 (68.5)	283 (65.4)
Renal-replacement therapy	46 (10.7)	42 (9.7)
Vasopressor infusion***	428 (99.8)	433 (100)

Septic shock definitie= Vasopressie + lactaat >2mmol/L

Uitkomsten

Table 2. Primary and Secondary Outcomes.*

Outcome	Vitamin C	Placebo	Treatment Effect (95% CI)†
Primary			
Death or persistent organ dysfunction at 28 days — no./total no. (%)‡	191/429 (44.5)	167/434 (38.5)	1.21 (1.04 to 1.40)
Death	152/429 (35.4)	137/434 (31.6)	1.17 (0.98 to 1.40)
Persistent organ dysfunction§	39/429 (9.1)	30/434 (6.9)	1.30 (0.83 to 2.05)
Vasopressor use	8/429 (1.9)	6/434 (1.4)	1.36 (0.48 to 3.85)
Mechanical ventilation	25/429 (5.8)	19/434 (4.4)	1.31 (0.74 to 2.30)
Renal-replacement therapy	24/429 (5.6)	18/434 (4.1)	1.35 (0.73 to 2.5)
Secondary			
Median no. of days without organ dysfunction in the ICU by day 28 (IQR)¶	17 (−1 to 25)	19.5 (−1 to 25)	−2.43 (−7.23 to 2.37)
Death by 6 mo — no./total no. (%)‖	191/417 (45.8)	185/426 (43.4)	1.14 (0.93 to 1.39)
EQ-5D-5L score at 6 mo¶**			
Score on visual-analogue scale	65.8±20.9	63.8±22.5	2.04 (−1.97 to 6.05)
Median dimension score (IQR)			
Mobility	2 (1–3)	2 (1–3)	−0.19 (−0.43 to 0.04)
Self-care	1 (1–2)	1 (1–2)	−0.07 (−0.29 to 0.15)
Usual activities	2 (2–4)	2 (2–3)	0.02 (−0.23 to 0.28)
Pain or discomfort	2 (1–3)	2 (1–3)	0.00 (−0.19 to 0.18)
Anxiety or depression	1 (1–2)	2 (1–2)	−0.08 (−0.24 to 0.09)
SOFA score¶††			
Day 1 (N=862)	10.2±3.4	10.1±3.7	0.05 (−0.42 to 0.53)
Day 2 (N=862)	9.9±5.2	9.5±5.1	0.39 (−0.30 to 1.07)
Day 3 (N=861)	9.2±6.0	9.0±6.0	0.23 (−0.57 to 1.03)
Day 4 (N=861)	8.7±6.5	8.7±6.6	−0.03 (−0.90 to 0.85)
Day 7 (N=862)	9.0±7.9	8.3±7.3	0.66 (−0.35 to 1.67)
Day 10 (N=277)	7.5±4.4	7.5±3.9	0.05 (−0.94 to 1.05)
Day 14 (N=191)	7.4±4.2	7.3±4.2	0.07 (−1.12 to 1.26)
Day 28 (N=56)	6.5±3.8	7.9±5.7	−1.42 (−3.98 to 1.14)
Safety outcomes — no./total no. (%)‡‡			
Stage 3 acute kidney injury	162/429 (37.8)	164/433 (37.9)§§	1.00 (0.85 to 1.19)
Acute hemolysis¶¶	0	0	NA
Hypoglycemia	26/429 (6.1)	22/433 (5.1)§§	1.25 (0.73 to 2.14)
Serious adverse events	1/429 (0.2)‖‖	0	NA

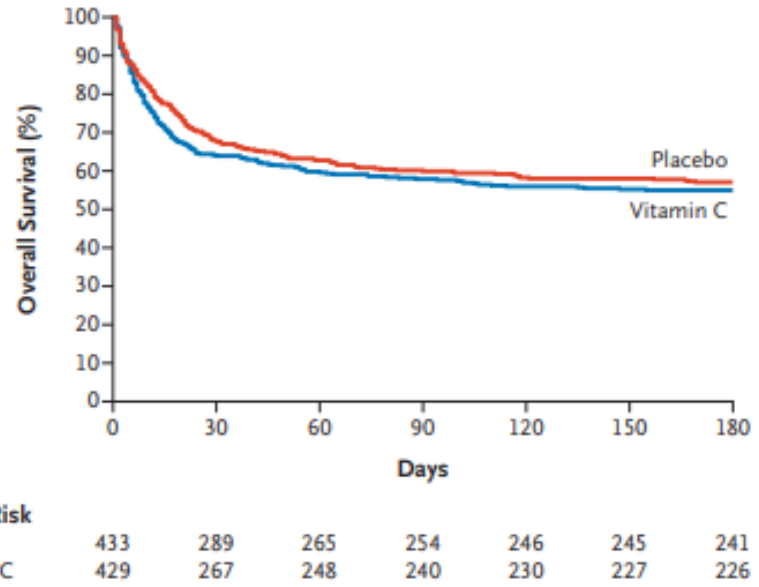
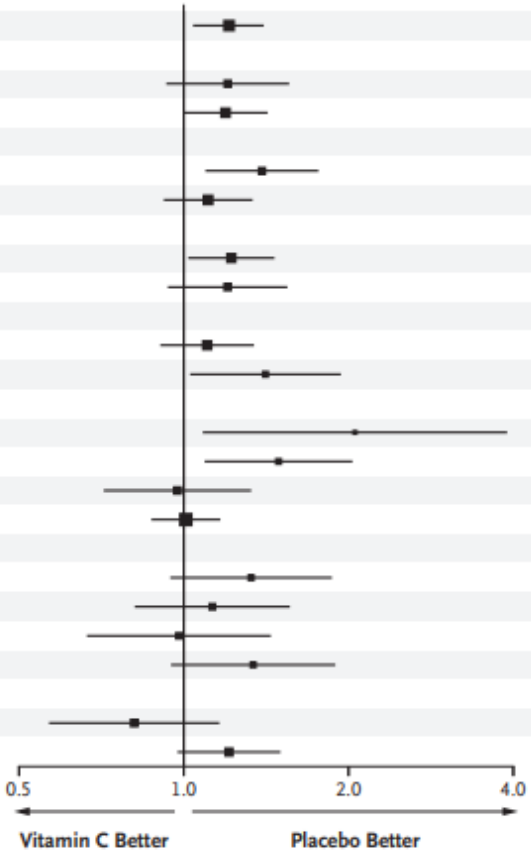


Figure 2. Kaplan–Meier Analysis of Survival at 6 Months.

Shown is the percentage of patients who were alive at the 6-month follow-up (226 patients [54.2%] in the vitamin C group and 241 [56.6%] in the placebo group), which was a secondary outcome in the trial.

Uitkomsten –subgroep analyse

Subgroup	Vitamin C	Placebo	Risk Ratio (95% CI)
	no. of events/total no.		
Overall	191/429	167/434	1.21 (1.04–1.40)
Age			
<65 yr	69/180	65/194	1.20 (0.93–1.56)
≥65 yr	122/249	101/239	1.19 (1.00–1.42)
Sex			
Female	72/151	62/173	1.39 (1.10–1.76)
Male	119/278	104/260	1.11 (0.92–1.34)
Clinical Frailty Scale			
1–4	133/312	114/308	1.22 (1.02–1.46)
≥5	58/117	51/124	1.20 (0.94–1.55)
Sepsis-3 definition of septic shock			
Yes	91/195	85/183	1.10 (0.91–1.34)
No	54/132	41/143	1.41 (1.03–1.94)
Predicted risk of death (%)			
Quartile 1 (8.5–31.9)	22/95	12/98	2.05 (1.08–3.90)
Quartile 2 (32.0–53.0)	55/117	39/118	1.49 (1.09–2.03)
Quartile 3 (53.1–70.0)	42/101	42/100	0.97 (0.71–1.33)
Quartile 4 (70.1–97.4)	72/116	73/117	1.01 (0.87–1.17)
Vitamin C level (μmol/liter)			
Quartile 1 (0.06–5.37)	44/92	27/71	1.33 (0.94–1.87)
Quartile 2 (5.38–12.38)	38/82	32/78	1.13 (0.81–1.56)
Quartile 3 (12.39–21.99)	26/72	35/90	0.98 (0.67–1.44)
Quartile 4 (22.00–1156.04)	35/78	30/83	1.34 (0.95–1.89)
SARS-CoV-2 infection			
Yes	19/37	18/26	0.81 (0.57–1.16)
No	172/392	148/407	1.21 (0.97–1.50)



Discussie

Onverwachte uitkomst

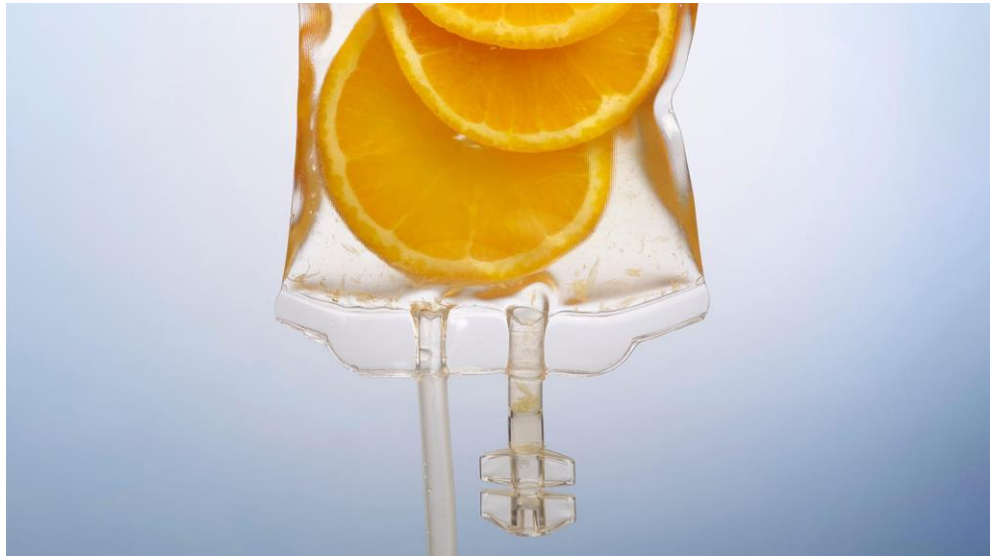
- Meer overlijden/ orgaanfalen op dag 28 bij gebruik vitamine C
- Geen duidelijke verklaring vanuit secundaire uitkomsten

Vergelijking eerder onderzoek

- CITRIS-ALI beademde patiënten> meer oxidatieve stress?
- Geen ARDS bij baseline gemeten

Event rate< expected 50% vs 38.5%

- Heb je dan de goede populatie? Timing/ ziekte



Discussie

Post-randomisation exclusions

- Levert dit selectie bias op?
- Independent committee/ information available before randomisation
- 1x randomisatie deferred consent, toch geweigerd, 5x surrogate consent en geweigerd, 1x allergie, 1x verkeerde studie gerandomiseerd, 1x consent ingetrokken door patiënt na infusie (ITT)

Discussie

Composite outcome

Rationale

- Klassiek ICU primair endpoint: 28 dagen mortaliteit
- Maar zijn infectie, QoL, orgaanschade niet belangrijker?
- Indien op dag 28 nog Persistent organ dysfunction (POD=MV, RRT of vasopressie) ook significant hogere mortaliteit.
- Dus levend op dag 28 is geen garant voor succes.

Voordeel

In combinatie zijn ze maximaal klinisch relevant

Sample size kan kleiner want event rate stijgt

Data op 1 dag gemeten > weinig missing data >>efficiëntere RCT

Kun je alles combineren?

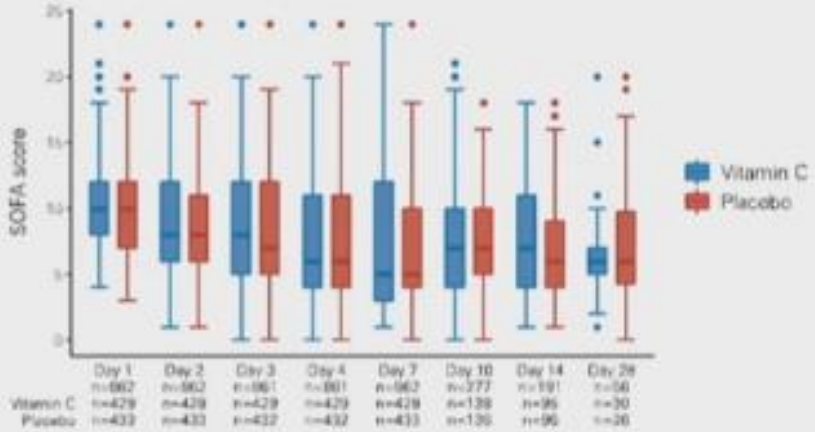
- Effect van de factoren moet zelfde kant uitgaan
- Factoren van gelijke belangrijkheid

Heyland et al. Critical Care 2011, 15:R98

Vragen?

Safety, SOFA, & biomarkers

Safety outcomes — no./total no. (%)	Vitamin C	Placebo	Treatment Effect (95% CI)†
Stage 3 acute kidney injury	162/429 (37.8)	164/433 (37.9)	1.00 (0.85 to 1.19)
Acute hemolysis	0	0	NA
Hypoglycemia	26/429 (6.1)	22/433 (5.1)	1.25 (0.73 to 2.14)
Serious adverse events	1/429 (0.2)	0	NA



Biomarker mean (SD)	Day 1		Day 3		Day 7	
	Vitamin C (n=333)	Placebo (n=329)	Vitamin C (n=294)	Placebo (n=292)	Vitamin C (n=207)	Placebo (n=208)
Dysoxia Lactate (mmol/L)	3.4 (1.7)	3.0 (1.8)	2.1 (1.7)	1.9 (1.7)	2.0 (1.6)	1.8 (1.6)
Inflammation IL-18 (pg/ml) TNF-α (pg/ml)	2.6 (4.3) 42.8 (72.5)	2.5 (7.0) 43.2 (97.2)	1.6 (1.8) 19.6 (19.9)	1.4 (1.4) 18.4 (23.8)	1.3 (2.6) 15.88 (18.0)	1.4 (1.7) 15.3 (14.5)
Endothelial injury TM (ng/ml) ANG-2 (pg/ml)	19.8 (13.6) 35660 (45374)	19.8 (17.4) 35463 (57098)	19.0 (13.4) 26816 (47249)	19.5 (17.3) 25482 (45919)	18.9 (12.5) 12070 (14657)	19.0 (11.7) 12851 (16570)