Clinical Nutrition 48 (2025) 153–160

Contents lists available at ScienceDirect

Clinical Nutrition

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

Original article

The impact of high versus standard enteral protein provision on functional recovery following intensive care admission: A pre-planned Bayesian analysis of the PRECISe trial

Eline Schouteden [a, b, 1], Samuel Heuts [c, d, 1], Julia LM. Bels [e, f], Steven Thiesen [a, b, g], Rob JJ. van Gassel [e, f, h], Zheng-Yii Lee [i], Christian Stoppe [j, k], Albertus Beishuizen [l], Ashley De Bie Dekker [m], Vincent Fraipont [n], Stoffel Lamote [o], Didier Ledoux [p, q], Clarissa Scheeren [r], Elisabeth De Waele [s], Arthur van Zanten [t, u], Sander MJ. van Kuijk [v], Marcel CG. van de Poll [d, e, h, *], Dieter Mesotten [a, b, w], Andrea Gabrio [x], the PRECISe study team

[a] Department of Intensive Care Medicine, Ziekenhuis Oost-Limburg, Genk, Belgium
[b] Faculty of Medicine and Life Sciences, UHasselt, Diepenbeek, Belgium
[c] Department of Cardiothoracic Surgery, Maastricht University Medical Center+, Maastricht, the Netherlands
[d] Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, the Netherlands
[e] Department of Intensive Care Medicine, Maastricht University Medical Center+, Maastricht, the Netherlands
[f] School for Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University, Maastricht, the Netherlands
[g] Department of Cardiovascular Sciences, Katholieke Universiteit Leuven, Leuven, Belgium
[h] Department of Surgery, Maastricht University Medical Center+, Maastricht, the Netherlands
[i] Department of Anaesthesiology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia
[j] Department of Cardiac Anesthesiology & Intensive Care Medicine, Charité Berlin, Germany
[k] Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, University Hospital Würzburg, Würzburg, Germany
[l] Intensive Care Center, Medisch Spectrum Twente, Enschede, the Netherlands
[m] Department of Intensive Care Medicine, Catharina Ziekenhuis Eindhoven, Eindhoven, the Netherlands
[n] Intensive Care Unit, Citadelle Hospital, Liège, Belgium
[o] Department of Intensive Care Medicine, Academisch Ziekenhuis Groeninge, Kortijk, Belgium
[p] Sensation and Perception Research Group, GIGA Consciousness, University of Liège, Liège, Belgium
[q] Intensive Care Units, University Hospital of Liège, Liège, Belgium
[r] Department of Intensive Care Medicine, Zuyderland Medisch Centrum, Heerlen, the Netherlands
[s] Department of Nutrition, Universitair Ziekenhuis Brussel, Jette, Belgium
[t] Department of Intensive Care Medicine, Gelderse Vallei Ziekenhuis, Ede, the Netherlands
[u] Division of Human Nutrition & Health, Wageningen University & Research, Wageningen, the Netherlands
[v] Department of Clinical Epidemiology and Medical Technology Assessment (KEMTA), Maastricht University Medical Center+, Maastricht, the Netherlands
[w] Clinical Trial Unit (Future Health), Ziekenhuis Oost-Limburg, Genk, Belgium
[x] Department of Methodology and Statistics, Maastricht University, Maastricht, the Netherlands

ARTICLE INFO

Article history:
Received 19 February 2025
Accepted 27 March 2025

Keywords:
Critical illness
Nutrition
High protein provision
Standard protein provision
Quality of life
Bayesian

SUMMARY

Background and aims: High protein nutrition may improve outcomes after critical illness. We recently published the primary frequentist analysis of the PRECISe trial, showing that high (2.0 g/kg/day) compared with standard (1.3 g/kg/day) protein provision led to statistically significant worse health-related quality of life. The study, however, was not powered to draw definitive conclusions about clinical and other functional outcomes under a frequentist framework. We present a pre-planned and pre-specified Bayesian analysis to facilitate the clinical interpretation of these paramount endpoints.
Methods: The trial enrolled 935 patients and used the EQ-5D-5L health utility score as the primary endpoint. We performed Bayesian analyses of the primary and selected secondary endpoints, and relevant subgroups, under weakly informative priors. Sensitivity analyses were performed using skeptical and enthusiastic priors, and informed priors (when available) based on existing literature. Thresholds for clinically relevant differences were predefined.

* Corresponding author. Department of Intensive Care Medicine Maastricht Universty Medical Center (MUMC+) P. Debyelaan 25, 6229HX, Maastricht, the Netherlands.
E-mail address: marcel.vande.poll@mumc.nl (M.CG. van de Poll).
[1] Shared first authors.

https://doi.org/10.1016/j.clnu.2025.03.022

Results: The posterior probability of benefit from high (2.0 g/kg/day) protein targets with respect to the EQ-5D-5L health utility score was 0 %. Concerning 60-day mortality, the posterior probability of any benefit from high protein provision was 8 %, with a posterior probability of clinically important harm (>5 % absolute risk difference) of 47 %, which varied between 1 and 21 % across various sensitivity analyses under reference or literature-based priors.
Conclusions: This pre-planned Bayesian re-analysis of the PRECISe trial shows that high (2.0 g/kg/day) compared to standard (1.3 g/kg/day) protein provision in critically ill patients has a low probability to yield any benefit and results in a high probability of an increase of 60-day mortality.
Registration number of clinical trial: NCT04633421.

1. Introduction

Critical illness is accompanied by acute and profound muscle loss, which is associated with a long-term reduction of health-related quality of life in intensive care unit (ICU) survivors [1,2]. It has been suggested that high protein nutrition can improve functional outcomes following ICU admission by mitigating net muscle loss. However, emerging high-quality evidence doubts the beneficial effects of high protein nutrition in critical illness [3–5].

We recently published the PRECISe trial, a pragmatic double-blinded, randomized controlled trial assessing the effect of high (2.0 g/kg/day) vs. standard (1.3. g/kg/day) enteral protein targets during ICU admission on functional recovery following ICU admission in critically ill patients. We found a statistically significant negative effect of high protein targets on health-related quality of life. Also, differences in other key endpoints and subgroups seemed to favor standard protein targets [3].

The analysis of the PRECISe trial was performed under a traditional frequentist statistical framework [6]. While seemingly easy to interpret, standard frequentist statistical approaches often lack sufficient power to draw meaningful conclusions from secondary and subgroup analyses, and cannot estimate the probability of clinically relevant treatment effects.

The Bayesian statistical framework offers an alternative approach to overcome the limitations posed by standard frequentist methods [7]. Consequently, we predefined a Bayesian analysis of the PRECISe trial, in a published protocol [8]. Here we present the results of this pre-planned and pre-specified Bayesian analysis of the PRECISe trial, with an additional focus on crucial secondary outcomes and subgroups [8].

2. Materials and methods

2.1. Study design

The PRECISe trial (NCT04633421) was an investigator-initiated, double-blind, multicenter, parallel-group, randomized controlled trial in five Belgian and five Dutch hospitals, comparing higher enteral protein provision (i.e., 2.0 g/kg per day) with standard enteral protein provision (i.e., 1.3 g/kg per day) in critically ill patients who are mechanically ventilated. The design of the trial has been extensively detailed elsewhere [6]. The primary outcome was health-related quality of life measured by the EuroQol-5 dimension 5-level health utility score (EQ-5D-5L HUS) over a period of 180 days following randomization. Patients were assessed at three time points (30, 90, and 180 days), and analyses were performed to take these longitudinal measurements into account. Secondary outcomes comprised 60-day survival, and physical tests such as handgrip strength and a 6-min walking test over 180 days. Subgroups were predefined based on the presence of acute kidney injury, sepsis, or severe multi-organ failure at randomization. The study was approved by the independent medical ethics committees of Maastricht University (METC 20–039) and University Hospital Brussels (2020/223).

2.2. Principles of Bayesian analyses

A cornerstone of Bayesian inference is the incorporation of prior beliefs about an effect estimate (the prior) into the newly obtained data (the likelihood), to calculate the posterior probability of the effect estimate (the posterior) [9]. Importantly, the robustness of the trial findings can subsequently be tested under various priors, including prior 'pessimistic', 'skeptical', and 'enthusiastic' views, in addition to prior that may be derived from previous literature (informed priors). Nevertheless, to optimize objectivity, a valid starting point to analyze data from an randomized trial, is the 'weakly informative prior' (assuming no difference between treatments, with large uncertainty).

Second, as the posterior is a probability distribution, it allows for the estimation of various treatment effect sizes, including clinically relevant ones. This concept is also known as the minimal clinically important difference (MCID).

For further reading and a more in-depth explanation of the merits and drawbacks of Bayesian statistical inference, we refer to explanatory reviews [9–11].

2.3. Rationale for the implementation of Bayesian inference in nutritional and critical care clinical trials

Clinical trials are often time- and resource-consuming, which has led investigators to base their sample size calculation on an (optimistic) expected treatment effect, rather than a clinically important treatment effect. When the null hypothesis is not rejected in these cases, this may be the consequence of a reduced power, and this might cause critical care physicians to abandon therapies that have a potentially clinically important benefit [4]. In contrast, the Bayesian frameworks allows the direct estimation of the posterior probability of any treatment effect, including the MCID. Finally, the incorporation of prior data may facilitate a more feasible sample size calculation, while the use of reference priors (such as enthusiastic and skeptical priors) can assess the robustness of the findings.

2.4. Bayesian analysis and protocol

The Bayesian re-analysis of the PRECISe trial was performed according to a pre-specified protocol and statistical analysis plan that was published before the database was locked [8]. In this protocol, the outcomes that were deemed of particular interest were defined, as well as the prior probabilities and the effect sizes that were considered to represent minimal clinically important differences (MCID). An overview of prior probabilities and MCIDs

can be found in the Supplemental Appendix (Table S1) and in the published protocol [8]. The Bayesian re-analysis was performed in agreement with the "Reporting of Bayes Used in Clinical Studies" guideline (ROBUST) [12].

2.5. Outcomes, minimal clinically important differences, and informative priors

The EQ-5D-5L HUS is a summary utility score derived from five health domains that are ranked on five-point Likert scales. Domain scores are translated to a utility score by nation-specific value sets. Hence, the lowest value representing the worst score on all domains varies among countries. For the PRECISe population, the EQ-5D-5L ranged from −0.5 to 1.0 (perfect health) [13]. This utility score is well-suited to study functional outcomes in critically ill populations with high mortality as it can handle death as a competing risk by assigning deceased patients a score of zero [14]. In line with the longitudinal design of the follow-up, we assessed the EQ-5D-5L HUS at 30, 90, and 180 days, in addition to the analysis of the overall (longitudinal) EQ-5D-5L HUS. No informative prior probabilities that were considered meaningful for the current Bayesian re-analyses were found in the literature [15].

2.6. Physical tests

Physical tests that were selected for this Bayesian re-analysis were handgrip strength and the 6-min walking test over 180 days. The 6-min walking test is considered to represent overall physical performance, and handgrip strength is feasible to perform by all patients, and has, unlike the MRC-sum score, no ceiling effect [16]. Minimal clinically important differences were 5.0 kg and 19 m respectively [17,18]. For neither test, meaningful literature-based prior probabilities were found [15].

2.7. Clinical outcomes

We predefined the clinical outcomes 60-day mortality and duration of mechanical ventilation as outcomes because of their clinical relevance, and as they were presented before in the EFFORT Protein trial and a subsequent meta-analysis [4,15], facilitating the formulation of informative priors. MCIDs were set at a predefined 5 % absolute risk reduction for 60-day mortality and 1.0 days for the duration of mechanical ventilation [19].

2.8. Prior probabilities

Weakly informative, skeptical, and enthusiastic priors were used for all endpoints. Weakly informative priors were centered around "no effect". This implied a mean of 0 and a standard deviation of 3 on the log OR scale for binary outcomes. For continuous outcomes, a mean of 0 and a standard deviation of 100 times the MCID was used. Skeptical and enthusiastic priors were defined following a modification of the approach suggested by de Grooth and Elbers [20]. Skeptical priors were designed to resemble a strong belief that the intervention exerts no effect. In contrast, enthusiastic priors were designed to resemble a strong belief that the intervention exerts a positive effect. Skeptical priors were centered at a mean difference (MD) or log OR of 0 (absolute risk difference (ARD) = 0). The distribution incorporates a <10 % probability that the estimated treatment effect will exceed +1 MCID [8]. Conversely, enthusiastic priors were centered around an effect of +2 MCID and follow a similar distribution with a probability of <10 % that the estimated effect size will be lower than +1 MCID.

2.9. Statistical analysis

The sample size of the PRECISe trial was determined at 935 patients, and was based on Monte Carlo simulations to have sufficient power for the primary frequentist analysis [3].

Posterior distributions obtained from Bayesian analyses were summarized in terms of mean differences (MDs, for continuous variables), mean absolute risk differences (ARDs), or median odds ratios (ORs), with corresponding 95 % credible intervals (CrIs). Posterior probabilities of various effect size thresholds were calculated based on the area under the curve of the posterior distribution. Consequently, posterior probabilities of any benefit, a clinically important benefit (ARD/MD > +1 MCID), or clinically important harm (ARD/MD < −1 MCID) are presented under a weakly informative prior. In addition, the distribution of the primary outcome was presented in a dedicated grid plot. The Bayesian analyses were performed in R (R Core Team, R Foundation, Vienna, Austria, version 4.3.1) using the R2jags package and Markov Chain Monte Carlo (MCMC) algorithms. Adequacy of model convergence was assessed through potential scale reduction factors (Rhat) effective sample size (ESS), and other diagnostics such as density and trace plots, while model fit was assessed through the deviance information criterion (DIC and other criteria alike in relative terms), and by use of posterior prediction checks (PPCs, in absolute terms).

3. Results

3.1. Bayesian analysis: EQ-5D-5L health utility score

Bayesian re-analysis of the primary endpoint in the intention-to-treat population over the entire follow-up period showed a mean difference in the EQ-5D-5L HUS of −0.05 (−0.07 to −0.02), resulting in a 0 % probability of any benefit (MD > 0), with respect to health-related quality of life (Table 1, Fig. 1). Considering the predefined MCID of 0.06, the risk of clinically relevant harm was calculated at 15 %. A post-hoc analysis estimating the posterior probabilities of harm across different effect sizes that are considered to be clinically relevant in the literature showed that the posterior probability of clinically relevant harm under a non-informative prior ranged from 4 % to 65 % (Supplementary Appendix, Table S2). The posterior probability of any benefit under a non-informative prior remained below 10 % at all individual follow-up moments (Table 1).

Subgroup analyses revealed a low posterior probability of a beneficial effect in patients both septic and non-septic patients and in patients with severe multi-organ failure. In non-septic patients, the posterior probability of clinically important harm was 56 %. In patients with acute kidney injury at the time of randomization, there was a 65 % posterior probability of any benefit but only a 4 % posterior probability of a clinically important benefit (Table 1).

3.2. Bayesian analysis: physical tests

Data were available from 287 to 400 of the 935 enrolled patients for the 6-min walking and handgrip strength tests, respectively. Results show that under a weakly informative prior, the posterior probability of any benefit was 100 % for the 6-min walking test and 7 % for the handgrip strength test, respectively. Instead, the posterior probability of a clinically important difference in favor of high protein was 100 % as well for the 6-min walking test, while it was 0 % for handgrip strength (Table 1).

Table 1
Primary Bayesian analysis of predefined outcomes and subgroups of the PRECISe trial under a minimally informative prior.

	Standard protein (n = 465)	High protein (n = 470)	Mean posterior ARD/MD (95 % CrI)	Mean odds ratio (95 % CrI)	Posterior probabilities		
					any benefit	clinically important benefit	clinically important harm
EQ-5D-5L HUI	0.43 (n = 430)	0.38 (n = 419)	−0.05 (−0.07, −0.02)	1.33 (1.08, 1.60)	0 %	0 %	15 %
EQ-5D-5L HUI 30 days	0.37 (n = 407)	0.33 (n = 398)	−0.04 (−0.09, 0.00)	1.32 (0.91, 1.75)	4 %	0 %	25 %
EQ_5D-5L HUI 90 days	0.43 (n = 396)	0.38 (n = 386)	−0.05 (−0.11, 0.01)	1.26 (0.89, 1.69)	5 %	0 %	34 %
EQ-5D-5L HUI 180 days	0.44 (n = 394)	0.40 (n = 393)	−0.04 (−0.1, 0.02)	1.29 (0.91, 1.69)	9 %	0 %	26 %
EQ-5D-5L HUI Sepsis	0.41 (n = 213)	0.38 (n = 202)	−0.03 (−0.07, 0.01)	1.34 (1.00, 1.69)	8 %	0 %	5 %
EQ-5D-5L HUI Non-sepsis	0.44 (n = 217)	0.38 (n = 217)	−0.06 (−0.10, −0.03)	1.32 (0.98, 1.70)	0 %	0 %	56 %
EQ-5D-5L HUI AKI	0.31 (n = 92)	0.32 (n = 96)	0.01 (−0.05, 0.07)	1.11 (0.74, 1.53)	65 %	4 %	1 %
EQ-5D-5L HUI Severe multi-organ failure	0.38 (n = 255)	0.34 (n = 244)	−0.03 (−0.07, 0.00)	1.42 (1.08, 1.76)	4 %	0 %	6 %
6MWT (meters)	64 (n = 154)	69 (n = 133)	27.4 (24.7, 30.1)	NA	100 %	0 %	0 %
HGS (kg)	77 (n = 212)	73 (n = 188)	−1.25 (−2.96; 0.48)	NA	7 %	0 %	0 %
Duration of mechanical ventilation (d)	14 (n = 450)	14 (n = 454)	1 (0, 2)	NA	10 %	0 %	44 %
60-day mortality	0.36 (n = 432)	0.40 (n = 428)	0.05 (−0.02, 0.1)	1.24 (0.89, 1.58)	8 %	0 %	47 %

ARD = absolute risk difference, MD = mean difference, CrI = credible interval, EQ-5D-5L HUI=EuroQoL-5D-5L health utility index, AKI = acute kidney injury, 6MWT = 6-min walking test, HGS = handgrip strength. Sepsis was defined according to sepsis-III criteria, AKI was defined using Kidney Disease: Improving Global Outcomes criteria, stage 1 or higher Severe multi-organ failure was defined using the Sequential Organ Failure Assessment score, severe organ failure is defined as ≥ median of the entire population.

3.3. Bayesian analysis: clinical outcomes

Bayesian analyses under a weakly informative prior showed a 10 % posterior probability of any beneficial effect from high protein provision on the duration of mechanical ventilation and an 8 % posterior probability of any beneficial effect on 60-day mortality. High protein provision resulted in a 44 % and 48 % posterior probability of clinically important harm with respect to the duration of mechanical ventilation and 60-day mortality (Table 1).

3.4. Bayesian sensitivity analyses under various priors

Sensitivity analyses under skeptical and enthusiastic priors were largely consistent with the primary analyses. They yielded a 0 % posterior probability of a clinically relevant beneficial effect of high protein provision for any endpoint or subgroup (Table 2), except for the subgroup with acute kidney injury at the time of randomization (posterior probability of clinically relevant benefit of 7 % under an enthusiastic prior), and, inherently, the 6-min walking test (100 %). Of note, under an enthusiastic prior (strongly favoring high protein), the probability of a clinically important harmful effect of high protein provision on 60-day mortality was only 8 %. Consequently, the relative insensitiveness of the posterior probabilities to the various predefined prior distributions confirms the robustness of the results of the PRECISe trial.

4. Discussion

The PRECISe trial was a double-blind multicenter randomized controlled trial that assessed the effect of high (2.0 g/kg/day) vs standard (1.3. g/kg/day) protein provision on functional outcome in critically ill patients. The probabilistic interpretation that is facilitated by the current Bayesian re-analysis corroborates the dichotomous conclusion of the primary frequentist analysis by showing a negligibly low probability of benefit and a notable high probability of clinically important harm of high protein provision in critically ill patients on various functional and clinical outcomes [3]. Most importantly, we found a high posterior probability of a clinically important increase in mortality that even persisted in various sensitivity analyses under a variety of predefined priors, including an enthusiastic prior belief towards the benefit of high protein nutrition, confirming the overall robustness of the results.

The PRECISe trial was primarily focused on functional and physical outcomes, but it also contained important results with respect to clinical outcome data. The frequentist analysis found a statistically significant reduction in the primary outcome, the EQ-5D-5L HUS in the high protein group, which is reflected in this Bayesian analysis by the 0 % posterior probability of any benefit of high protein provision in critically ill patients with respect to health-related quality of life, even across all different types of prior distributions examined. Importantly, these posterior probabilities persisted in the predefined sensitivity analyses under various priors.

Traditional frequentist analyses of secondary endpoints and subgroups are often hindered by low statistical power, smaller sample sizes, and failure to adjust for multiplicity, which can lead to erroneous interpretation of their results and possible premature dismissal of potentially valuable data [7,21]. In this context, Bayesian analysis of such secondary outcomes can provide a powerful instrument to facilitate clinical interpretation of results that are prone to type-II error when dichotomized under a frequentist framework. Regarding 60-day mortality, our Bayesian analysis showed an 8 % posterior probability of any benefit of high protein provision and, hence, a 92 % probability of a harmful effect. Using the predefined minimal clinically important difference of 5 % absolute mortality reduction, we estimated a posterior probability of a clinically relevant benefit of high protein provision of 0 %, while we found a posterior probability of clinically relevant harm of 47 %. Still, it may be argued that the threshold for clinical relevance of an intervention as simple as modulating nutritional protein is even lower than 5 %. Consequently, lower thresholds for the MCID would inherently only further increase the posterior probability of clinically important harm under a weakly informative prior. Sensitivity analyses under skeptical, enthusiastic, and literature-based priors showed similar estimations, with a low posterior probability of a clinically important benefit and a substantial posterior probability of clinically important harm. Of note, the results on the outcome duration of mechanical ventilation were comparable with those on 60-day mortality.

The results of this Bayesian analysis thus further point to the potentially detrimental effects of excessive protein provision in critically ill patients. This is not only with respect to the speed of recovery, as was already shown by the primary analysis or the PRECISe trial, but also with respect to clinical endpoints such as mortality and duration of mechanical ventilation, as suggested by

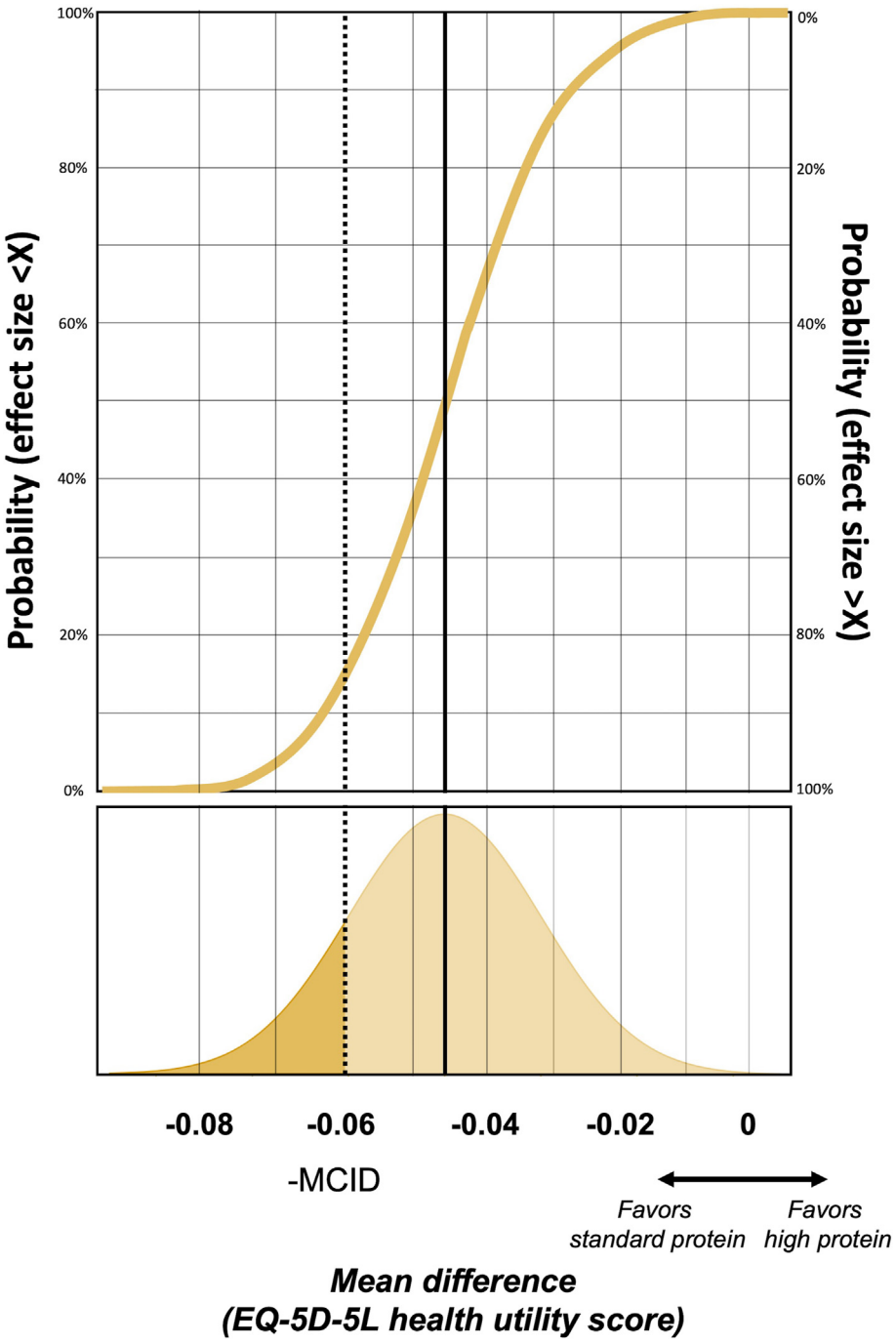

Fig. 1. Distribution of posterior probabilities for the mean difference in the primary outcome (EQ-5D-5L health utility score) under a weakly informative prior. The posterior follows a normal distribution, which can be appreciated in the lower part of the figure. Based on this probability distribution function, the non-linear function in the upper part of the figure can be derived. Consequently, this function corresponds with the posterior probability of a certain treatment effect size. For example, the grid plot represents that a 0.04 mean difference on the EQ-5D-5L scale in favor of standard protein (−0.04) intersects with the function at the level of 65 %-probability, implying that the posterior probability of a 0.04 mean difference, or greater, in favor of standard protein is 65 %. Of note, the probability distribution is almost completely located to the left of '0' mean difference. Finally, the dark-shaded area of the posterior distribution reflects the posterior probability of clinically relevant harm.

this Bayesian analysis. These findings are in line with those of the EFFORT Protein trial, which also studied the effect of high (≥2.2 g/kg/day) versus standard (1.2 g/kg/day) protein targets in critically ill patients, either through enteral or parenteral provision [4]. The Bayesian analysis of the EFFORT Protein trial found a posterior probability of 57–78 % increased 60-day mortality with high protein provision and an 11–25 % posterior probability of clinically important harm with regard to 60-day mortality (set at an absolute risk difference of 2 %) [22].

Some results of the current analysis may seem incongruent with the main trial report's overall clinical conclusions. For example, the posterior probability of any (and a clinically relevant) benefit of high protein provision with regard to the 6-min walking test was 100 %. This observation is in line with the results from the

Table 2
Bayesian sensitivity analyses of the various endpoints under skeptical, enthusiastic, and literature-based priors.

	Skeptical prior			Enthusiastic prior			Literature-based prior		
	Mean posterior ARD/MD (95 % CrI)	Posterior probabilities		Mean Posterior ARD/MD (95 % CrI)	Posterior probabilities		Mean posterior ARD/MD (95 % CrI)	Posterior probabilities	
		clinically important benefit	clinically important harm		clinically important benefit	clinically important harm		clinically important benefit	clinically important harm
EQ-5D-5L HUI	−0.05 (−0.07, −0.02)	0 %	14 %	−0.04 (−0.07, −0.01)	0 %	7 %	NA	NA	NA
5Q-5D-5L HUI 30 days	−0.04 (−0.09, 0.01)	0 %	20 %	−0.02 (−0.07, 0.02)	0 %	4 %	NA	NA	NA
EQ-5D-5L HUI 90 days	−0.05 (−0.10, 0.01)	0 %	30 %	−0.03 (−0.08, 0.03)	0 %	11 %	NA	NA	NA
EQ-5D-5L 180 days	−0.04 (−0.10, 0.02)	0 %	26	−0.02 (−0.08, 0.03)	0 %	11 %	NA	NA	NA
EQ-5D-5L HUI Sepsis	−0.03 (−0.07, 0.01)	0 %	6 %	−0.02 (−0.06, 0.02)	0 %	2 %	NA	NA	NA
EQ-5D-5L HUI Non-sepsis	−0.06 (−0.10, −0.02)	0 %	49 %	−0.05 (−0.09, −0.02)	0 %	33 %	NA	NA	NA
EQ-5D-5L AKI	0.01 (−0.05, 0.06)	3 %	1 %	0.02 (−0.04, 0.07)	7 %	0 %	NA	NA	NA
EQ-5D-5L HUI Severe multi-organ failure	−0.03 (−0.07, 0.00)	0 %	6 %	−0.03 (−0.06, 0.01)	0 %	3 %	NA	NA	NA
6MWT (meter)	27.2 (24.5, 29.8)	100 %	0 %	27.5 (24.8, 30.1)	100 %	0 %	NA	NA	NA
HGS (kg)	−1.21 (−2.97; 0.50)	0 %	0 %	−0.73 (−2.42; 0.96)	0 %	0 %	NA	NA	NA
Duration of mechanical ventilation (days)	1 (0, 2)	0 %	18 %	0 (−1, 1)	1 %	10 %	0 (−1, 0)	0 %	0 %
60-day mortality	0.03 (−0.02, 0.08)	0 %	21 %	0.01 (−0.04, 0.06)	8 %	1 %	0.01 (−0.03, 0.05)	0 %	2 %

ARD = absolute risk difference, MD = mean difference, CrI = credible interval, EQ-5D-5L HUI=EuroQoL-5D-5L health utility index, AKI = acute kidney injury, 6MWT = 6-min walking test, HGS = handgrip strength. Sepsis was defined according to sepsis-III criteria. AKI was defined using Kidney Disease: Improving Global Outcomes criteria, stage 1 or higher Severe multi-organ failure was defined using the Sequential Organ Failure Assessment score, severe organ failure is defined as ≥ median of the entire populatio

frequentist analysis, showing a statistically significant longer 6-min walking distance in patients allocated to high protein provision. However, it must be noted that the number of patients able and willing to perform the 6-min walking test at any moment during follow-up was quite small (<31 % of all enrolled patients), making this outcome susceptible to attrition bias.

Another striking result is the apparent benefit from high protein provision with respect to the primary endpoint in patients with acute kidney injury. This specific subgroup was selected in the pre-specified Bayesian analysis plan since, both in the EFFORT Protein trial as well as in a subsequent meta-analysis, high protein provision appeared to be particularly harmful in the presence of acute kidney injury [15,23]. These diverging results may be explained by differences in the definition of the "acute kidney injury" subgroups between the EFFORT Protein and PRECISe trials. In the PRECISe trial, patients were allocated to subgroups based on characteristics present at the time of randomization. In contrast, in the EFFORT Protein trial, patients were allocated to the "acute kidney injury" subgroup when they developed acute kidney injury in the first seven days after randomization. Consequently, this difference hampers direct comparability of these specific subgroups between trials. The fact that patients who developed acute kidney injury after randomization were allocated to the "no acute kidney injury" group may have underestimated the detrimental effect of high protein provision in the PRECISe trial. On the other hand, post-randomization subgroup allocation may have introduced bias in the EFFORT Protein trial by a possible effect of high protein provision on the development and severity of acute kidney injury [24]. The posterior probability of a clinically important beneficial effect of high protein provision in patients with acute kidney injury at the time of randomization is still only 7 % under an enthusiastic prior.

The current re-analysis, therefore, provides no ground to advocate for high protein provision in critically ill patients with acute kidney injury.

4.1. Limitations

The current study has several limitations, which are generally in line with the limitations of the primary analysis. First, we gave priority to achieving protein targets over energy targets. To this end, we did not account for the use of non-nutritional calories. Post-hoc analyses, however, showed that energy overfeeding was limited and did not differ significantly between both groups [3]. The limited number of patients completing physical tests, particularly the 6-min walking test, indicates severe bias and impairs the interpretability of these results. In addition, the predefined Bayesian protocol did not take into account several subgroups that seemed of after the analysis and publication of the frequentist report, such as subgroups based on sex or admission type (surgical/medical). Finally, any Bayesian analysis incorporating a spectrum of priors is susceptible to perceived subjectivity. In order to mitigate this potential limitation, we pre-specified the Bayesian protocol in a statistical analysis plan. Preceding the database lock, objective and reproducible priors were predefined, which is also reflected by their direction towards harm and benefit. Consequently, we have tried to eliminate bias in the elicitation of priors and MCIDs, and this conduct also agrees with Bayesian reporting guidelines.

5. Conclusion

In conclusion, this Bayesian analysis of the PRECISe trial further supports the notion that high protein provision targets (2.0 g/kg/day) do not improve functional outcome in critically ill patients and may even lead to a clinically important reduction in health-related quality of life. In addition, high protein targets lead to a substantial

probability of increased mortality in critical ill patients. Future research should establish more prospective evidence to substantiate guideline recommendations on beneficial and safe protein targets.

Author contribution

The PRECISe trial was designed by DM, RVG and MVDP and coordinated by JB under the supervision of MVDP and DM. AB, ADBD, VF, SL, DL, CS, EDW, AVZ and ST are investigators at the study sites. SVK is the trial statistician and performed frequentist analyses. Bayesian analyses were performed by AG, SH and ES. All authors reviewed and edited the drafts of the current manuscript and approved the final version. The first version of the manuscript was drafted by ES and MVDP. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

Data collected for this study will not be publicly available due to privacy regulations. Related documents (study protocol, Statistical Analysis Plan including data dictionary, clinical study report, and statistical analysis codes) are available online. Deidentified individual participant data will be made available to researchers or other organizations upon reasonable request through a written proposal directed to marcel.vande.poll@mumc.nl and dieter.mesotten@zol.be from six months after publication. Each proposal will be judged on relevance and methodological appropriateness by the senior authors. Before transferring the data, requestors must sign a data transfer agreement with a fully approved protocol and publication policy.

Funding statement

This report is independent research funded by the Netherlands Organisation for Healthcare Research and Development (ZonMw) and the Belgian Health Care Knowledge Centre (KCE) ([BENEFIT], The impact of high versus standard protein provision on functional recovery following Intensive Care admission: a randomised controlled, multicentre, parallel-group trial in mechanically ventilated, critically ill patients [Reference number 80-85200-98-18574]). The views expressed in this publication are those of the author(s) and not necessarily those of ZonMw or the Belgian Health Care Knowledge Centre, or the Department of Health. Blinded study feeds were provided in kind by Nutricia Research.

Conflict of interest

EDW reports honoraria for scientific lectures from Baxter Healthcare, Nutricia/Danone, and Nestlé. AVZ reports grants from AOP Pharma, Danone/Nutricia, Fresenius-Kabi, PAION and Rousselot; Consulting fees from AOP Pharma, Medcaptain, and PAION; Honoraria for lectures from Abbott, AOP Pharma, Baxter, Nestlé, Danone/Nutricia, Fresenius Kabi, GE Healthcare and Dutch Medical Food; Support for travel from Danone/Nutricia and Dutch Medical Food; and membership of the ESPEN adult ICU patient nutrition guideline committee, Executive Team SepsisNet Netherlands, Executive Team NESPEN, and the ESICM Section Feeding, Rehabilitation Endocrinology and Metabolism (FREM) as chair. MVDP reports grants from the Netherlands Organisation of Health Research and Development (ZonMW) and the Belgian Knowledge Centre for Healthcare (KCE), in-kind support from Nutricia; Consulting fees from Nutricia and Nestlé, and honoraria for lectures and support for travel from Nutricia.

All other authors (ES, SH, ST, JB, RVG, AB, ADBD, VF, SL, DL, CS, SVK, DM, AG) declare no competing interests.

Acknowledgement

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2025.03.022.

References

[1] van Gassel RJJ, Baggerman MR, van de Poll MCG. Metabolic aspects of muscle wasting during critical illness. Curr Opin Clin Nutr Metab Care 2020;23:96–101.
[2] Casaer MP, Wilmer A, Hermans G, Wouters PJ, Mesotten D, Van den Berghe G. Role of disease and macronutrient dose in the randomized controlled EPaNIC trial: a post hoc analysis. Am J Respir Crit Care Med 2013;187:247–55.
[3] Bels JLM, Thiessen S, van Gassel RJJ, Beishuizen A, De Bie Dekker A, Fraipont V, et al. Effect of high versus standard protein provision on functional recovery in people with critical illness (PRECISe): an investigator-initiated, double-blinded, multicentre, parallel-group, randomised controlled trial in Belgium and The Netherlands. Lancet 2024;404:659–69.
[4] Heyland DK, Patel J, Compher C, Rice TW, Bear DE, Lee ZY, et al. The effect of higher protein dosing in critically ill patients with high nutritional risk (EFFORT Protein): an international, multicentre, pragmatic, registry-based randomised trial. Lancet 2023;401:568–76.
[5] Heuts S, Lee ZY, Lew CCH, Bels JLM, Gabrio A, Kawczynski MJ, et al. Higher versus lower protein delivery in critically ill patients: a systematic review and bayesian meta-analysis. Crit Care Med 2025;53:e645–55.
[6] van Gassel RJJ, Bels JLM, Tartaglia K, van Bussel BCT, van Kuijk SMJ, Deane AM, et al. The impact of high versus standard enteral protein provision on functional recovery following intensive care admission (PRECISE trial): study protocol for a randomized controlled, quadruple blinded, multicenter, parallel group trial in mechanically ventilated patients. Trials 2023;24:416.
[7] Granholm A, Alhazzani W, Derde LPG, Angus DC, Zampieri FG, Hammond NE, et al. Randomised clinical trials in critical care: past, present and future. Intensive Care Med 2022;48:164–78.
[8] Heuts S, de Heer P, Gabrio A, Bels JLM, Lee ZY, Stoppe C, et al. The impact of high versus standard enteral protein provision on functional recovery following intensive care admission: protocol for a pre-planned secondary Bayesian analysis of the PRECISe trial. Clin Nutr ESPEN 2024;59:162–70.
[9] Heuts S, Kawczynski MJ, Sayed A, Urbut SM, Albuquerque AM, Mandrola JM, et al. Bayesian analytical methods in cardiovascular clinical trials: why, when, and how. Can J Cardiol 2025;41:30–44.
[10] Yarnell CJ, Abrams D, Baldwin MR, Brodie D, Fan E, Ferguson ND, et al. Clinical trials in critical care: can a Bayesian approach enhance clinical and scientific decision making? Lancet Respir Med 2021;9:207–16.
[11] Zampieri FG, Casey JD, Shankar-Hari M, Harrell Jr FE, Harhay MO. Using bayesian methods to augment the interpretation of critical care trials. An overview of theory and example reanalysis of the alveolar recruitment for acute respiratory distress syndrome trial. Am J Respir Crit Care Med 2021;203:543–52.
[12] Sung L, Hayden J, Greenberg ML, Koren G, Feldman BM, Tomlinson GA. Seven items were identified for inclusion when reporting a Bayesian analysis of a clinical study. J Clin Epidemiol 2005;58:261–8.
[13] EuroQol Research Foundation. EQ-5D-5L User Guide. Available from:: https://euroqolorg/publications/user-guides.
[14] Granholm A, Anthon CT, Kjaer MN, Maagaard M, Kaas-Hansen BS, Sivapalan P, et al. Patient-important outcomes other than mortality in contemporary ICU trials: a scoping review. Crit Care Med 2022;50:e759–71.
[15] Lee ZY, Dresen E, Lew CCH, Bels J, Hill A, Hasan MS, et al. The effects of higher versus lower protein delivery in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials with trial sequential analysis. Crit Care 2024;28:15.
[16] Davies TW, Kelly E, van Gassel RJJ, van de Poll MCG, Gunst J, Casaer MP, et al. A systematic review and meta-analysis of the clinimetric properties of the core outcome measurement instruments for clinical effectiveness trials of nutritional and metabolic interventions in critical illness (CONCISE). Crit Care 2023;27:450.
[17] Bohannon RW. Minimal clinically important difference for grip strength: a systematic review. J Phys Ther Sci 2019;31:75–8.
[18] Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. J Am Geriatr Soc 2006;54:743–9.
[19] Abrams D, Montesi SB, Moore SKL, Manson DK, Klipper KM, Case MA, et al. Powering bias and clinically important treatment effects in randomized trials of critical illness. Crit Care Med 2020;48:1710–9.

[20] de Grooth HJ, Elbers P. Pick your prior: scepticism about sceptical prior beliefs. Intensive Care Med 2022;48:374–5.
[21] Heuts S, Kawczynski MJ, Sayed A, Urbut SM, Albuquerque AM, Mandrola JM, et al. Bayesian analytical methods in cardiovascular clinical trials: why, when, and how. Can J Cardiol 2024.
[22] Haines RW, Granholm A, Puthucheary Z, Day AG, Bear DE, Prowle JR, et al. The effect of high protein dosing in critically ill patients: an exploratory, secondary Bayesian analyses of the EFFORT Protein trial. Br J Anaesth 2024;133:1192–200.
[23] Stoppe C, Patel JJ, Zarbock A, Lee ZY, Rice TW, Mafrici B, et al. The impact of higher protein dosing on outcomes in critically ill patients with acute kidney injury: a post hoc analysis of the EFFORT protein trial. Crit Care 2023;27:399.
[24] Hirji KF, Fagerland MW. Outcome based subgroup analysis: a neglected concern. Trials 2009;10:33.