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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

[a] Center for Translational Research in Aging & Longevity, Department of Health & Kinesiology, Texas A&M University, 1700 Research Parkway, College Station, TX 77845, USA
[b] Department of Family Medicine, Medical University of South Carolina, 5 Charleston Center Dr, Charleston, SC, USA
[c] Brody School of Medicine, East Carolina University, 600 Moye Blvd, Greenville, NC, USA
[d] Abbott Nutrition, Research and Development, 3300 Stelzer Rd, Columbus, OH, USA
[e] Department of Food Science and Human Nutrition, University of Illinois at Urbana-Champaign, 905 S. Goodwin Ave, Urbana, IL, USA
[f] Division of Endocrinology, Metabolism and Lipids, Emory University School of Medicine, 1648 Pierce Dr NE, Atlanta, GA, USA

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SUMMARY

Background: Hospitalized, malnourished older adults have a high risk of readmission and mortality.
Objective: Evaluation of a high-protein oral nutritional supplement (HP-HMB) containing beta-hydroxy-beta-methylbutyrate on postdischarge outcomes of nonelective readmission and mortality in malnourished, hospitalized older adults.
Design: Multicenter, randomized, placebo-controlled, double-blind trial.
Setting: Inpatient and posthospital discharge.
Patients: Older (≥65 years), malnourished (Subjective Global Assessment [SGA] class B or C) adults hospitalized for congestive heart failure, acute myocardial infarction, pneumonia, or chronic obstructive pulmonary disease.
Interventions: Standard-of-care plus HP-HMB ($n = 328$) or a placebo supplement ($n = 324$), 2 servings/day.
Measurements: Primary composite endpoint was 90-day postdischarge incidence of death or nonelective readmission. Other endpoints included 30- and 60-day postdischarge incidence of death or readmission, length of stay (LOS), SGA class, body weight, and activities of daily living (ADL).
Results: The primary composite endpoint was similar between HP-HMB (26.8%) and placebo (31.1%). No between-group differences were observed for 90-day readmission rate, but 90-day mortality was significantly lower with HP-HMB relative to placebo (4.8% vs. 9.7%; relative risk 0.49, 95% confidence interval [CI], 0.27 to 0.90; $p = 0.018$). The number-needed-to-treat to prevent 1 death was 20.3 (95% CI: 10.9, 121.4). Compared with placebo, HP-HMB resulted in improved odds of better nutritional status (SGA class, OR, 2.04, 95% CI: 1.28, 3.25, $p = 0.009$) at day 90, and an increase in body weight at day 30 ($p = 0.035$). LOS and ADL were similar between treatments.
Limitations: Limited generalizability; patients represent a selected hospitalized population.
Conclusions: Although no effects were observed for the primary composite endpoint, compared with placebo HP-HMB decreased mortality and improved indices of nutritional status during the 90-day observation period.
Clinical trial registration: www.ClinicalTrials.gov NCT01626742.

Abbreviations: ADL, activities of daily living; AMI, acute myocardial infarction; CHF, congestive heart failure; CI, confidence interval; COPD, chronic pulmonary obstructive disease; HMB, beta-hydroxy-beta-methylbutyrate; HP-HMB, high-protein beta-hydroxy-beta-methylbutyrate; ITT, intention-to-treat; LBM, lean body mass; LOS, length of stay; LS, least squares; MMSE, Mini Mental State Examination; NNT, number needed to treat; NOURISH, Nutrition effect On Unplanned ReadmIssions and Survival in Hospitalized patients; ONS, oral nutritional supplements; PNA, pneumonia; QoL, quality of life; SD, standard deviation; SE, standard error; SGA, Subjective Global Assessment.

* Corresponding author. Tel.: +1 979 220 2910; fax: +1 979 862 3244.
E-mail addresses: nep.deutz@ctral.org (N.E. Deutz), matheson@musc.edu (E.M. Matheson), mataresel@ecu.edu (L.E. Matarese), Menghua.Luo@abbott.com (M. Luo), geraldine.baggs@abbott.com (G.E. Baggs), jeffrey.l.nelson@abbott.com (J.L. Nelson), Refaat.Hegazi@abbott.com (R.A. Hegazi), tappende@illinois.edu (K.A. Tappenden), tzieg01@emory.edu (T.R. Ziegler).

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1. Introduction

Hospitalized older adults (≥65 years) are at high risk of malnutrition [1], which has a negative impact on subsequent clinical and economic outcomes, including a greater risk of mortality and a high rate of nonelective hospital readmission [2]. In particular, malnutrition at hospital admission is an independent predictor of subsequent hospital readmission [3] and is associated with higher mortality after hospital discharge [4].

Even short hospitalizations in older adults may have clinical consequences, such as loss of lean body mass (LBM) with accelerated functional decline [5]. This loss of LBM involves dysfunction of several cellular and physiologic processes [6] and may be exacerbated by malnutrition [7]. Patients often continue to lose body weight and LBM after hospital discharge, further adversely affecting outcomes [8].

Studies have shown that the use of oral nutritional supplements (ONS) in malnourished patients in community and hospital settings may reduce complications, mortality, and hospital readmissions [9–11]. While the prevalence of malnutrition is high [1], in a retrospective analysis of data over 11 years, only 1.6% of inpatient episodes out of 44.0 million involved ONS use [10]. In older patients, the effects of ONS have been extensively studied and have been consistently shown to increase body weight and improve nutritional status [11]. However, effects of ONS on readmission rates and mortality specifically in older adults have only been evaluated in small- to medium-sized trials, often involving heterogeneous populations [11–13]. While systematic reviews suggested that high-protein ONS (providing ≥20% total calories from protein) significantly reduced readmissions [14] and mortality [11] compared with controls, other systematic reviews and meta-analyses failed to show consistent results [12,13]. Thus, the efficacy of ONS on readmission and mortality in hospitalized, older adults remains uncertain.

Targeted ONS strategies for maintaining or protecting nutritional status in older adults have used a variety of supplements with different components including vitamin D, higher caloric content, amino acids, protein, and beta-hydroxy-beta-methylbutyrate (HMB) [14–16]. In particular, a role for supplemental protein has been suggested, since increased protein intake has been associated with improvement in LBM [17]. HMB, which is found naturally in the diet at very low levels and is an active metabolite of leucine, has been shown to regulate muscle protein metabolism with evidence supporting its safety and ability to prevent LBM loss during bed rest [18] and in patients with chronic diseases [15]. The current study evaluated a specialized, nutrient-dense ONS, containing both a high-protein content and HMB (HP-HMB), on postdischarge outcomes including nonelective readmission and mortality in initially hospitalized, malnourished, older adults. Eligible patients were those admitted for congestive heart failure (CHF), acute myocardial infarction (AMI), pneumonia (PNA), or chronic obstructive pulmonary disease (COPD), conditions previously shown to result in a high risk of 30-day readmission [19,20].

2. Methods

2.1. Study design

The NOURISH (Nutrition effect On Unplanned ReadmIssions and Survival in Hospitalized patients) study was a multicenter, prospective, randomized, double-blind, placebo-controlled, parallel-group study conducted in the United States between May 2012 and October 2014 (Fig. 1A). The study evaluated the effects of HP-HMB on the postdischarge incidence of hospital readmission, nutritional status indices and morbid events in older hospitalized adults. As per the initial protocol, the incidence of nonelective readmission within 90 days postdischarge was the primary outcome. Since death, which was a safety endpoint, and readmission are competing events, the composite event of death or nonelective readmission within 90 days postdischarge was defined as the primary efficacy endpoint. This definition was incorporated into the finalized statistical analysis plan subsequent to the interim analysis and prior to unblinding of the data; the sequence of finalization was consistent with Food and Drug Administration guidance and International Conference on Harmonisation guidelines.

During hospitalization, patients received the individual hospitals' standard nutritional care at the discretion of the attending physicians. Patients were instructed to consume 2 servings of their allocated study intervention (ie, HP-HMB or placebo) each day. During the 90-day postdischarge period, patients were instructed to continue to supplement their regular dietary intake with 2 servings daily of their allocated intervention, which was provided to the patients without charge. In order to maintain the blind, HP-HMB and placebo were packaged in identical Tetra Paks® identified only by product codes that were blinded to study investigators and sites; opaque straws were provided and used for consumption. Two flavors were available for each arm; patients were exposed only to the flavors of the assigned study arm product.

Patient assessments were performed at days 30, 60, and 90 or at study discontinuation and included intake of allocated intervention, morbidity, readmissions, functional and nutritional status, use of medications/dietary supplements, quality-of-life indices, medical care utilization, and adverse events (Fig. 1A). Blood was drawn at baseline and days 30 and 60. Additional contact via home visit or telephone was performed weekly to encourage compliance and collect information on morbid events, medical-care utilization and intake of allocated intervention, which were recorded by the patient in a provided record handbook. At the time of each clinical visit, the record was returned to the site coordinator to assess product intake compliance.

The protocol received approval from the appropriate site Institutional Review Board. All patients provided written informed consent.

2.2. Patients

Eligible patients were aged ≥65 years with a recent hospital admission (within 72 h) with a primary diagnosis of CHF, AMI, PNA, or COPD. Patients were required to have a Subjective Global Assessment (SGA) class of B (moderate or suspected malnutrition) or C (severe malnutrition); SGA is a validated tool that is considered the gold standard for assessment of malnutrition in hospitalized patients. All site personnel were trained on SGA and an instruction video was provided. Exclusion criteria were diabetes mellitus (type 1 or 2) due to product composition not intended for patients with diabetes mellitus; current active or treated cancer, and impaired renal or liver function. For details, see the Study Inclusion and Exclusion Criteria section (Supplementary Table 1).

Sites prescreened patients per hospital protocol, which ranged from screening all hospital admissions daily to reviewing computer-generated lists. If at least 1 eligibility criterion was not met, the reason was recorded and the patient was excluded.

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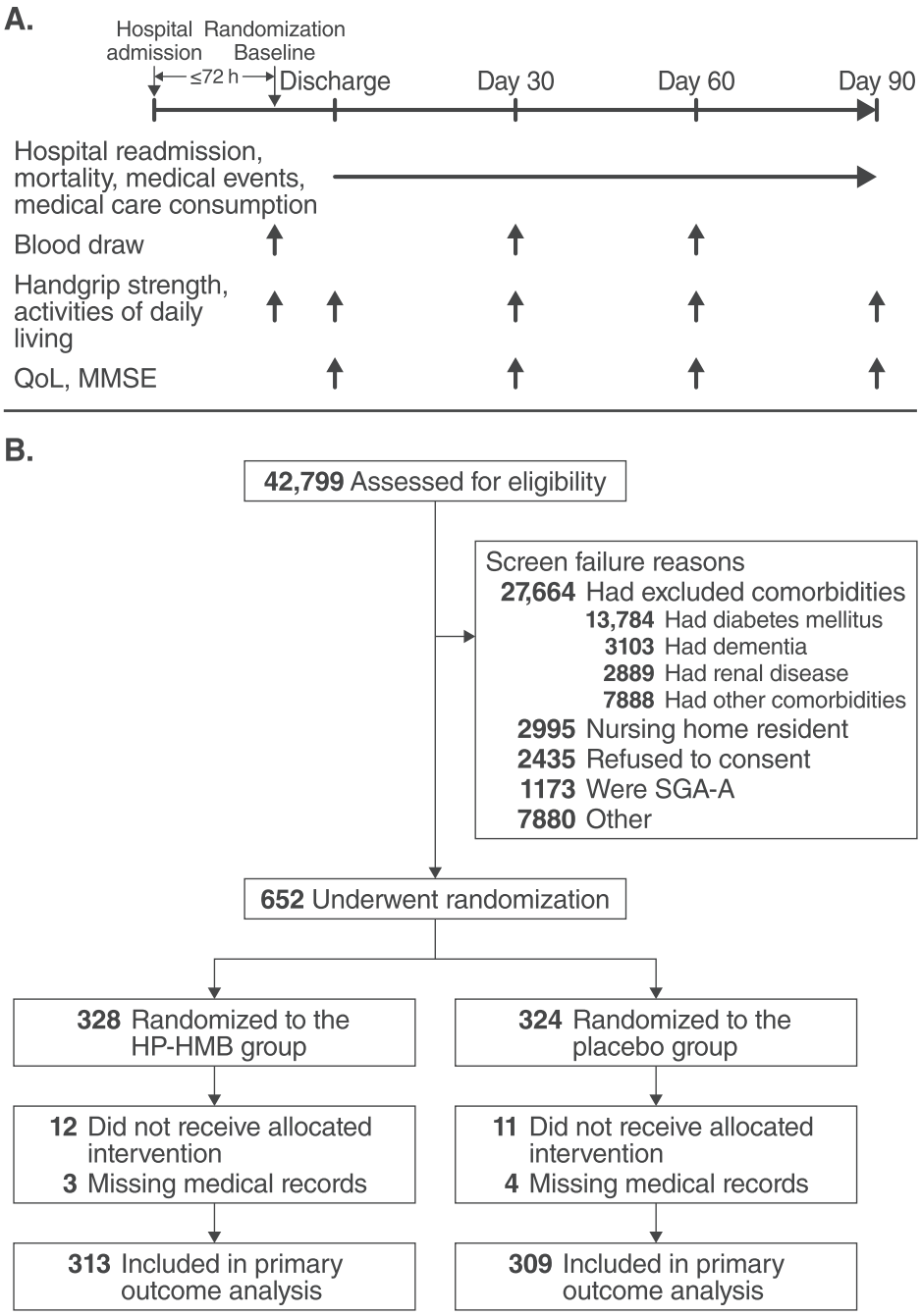

Fig. 1. Study design and numbers of patients enrolled and included in the analysis. Panel A shows the study design, and Panel B the numbers of patients who were assessed for eligibility, randomly assigned to either the specialized, nutrient-dense oral nutritional supplement, HP-HMB, or placebo, and included in the analysis. For patients who were lost to follow-up (18 and 19 patients in HP-HMB and placebo, respectively), their time to last study contact was used in the primary analysis (Panel B). HP-HMB, high-protein beta-hydroxy-beta-methylbutyrate; MMSE, Mini Mental State Examination; QoL, quality of life; SGA, Subjective Global Assessment.

2.3. Study treatments

Patients were randomized (1:1) through a centralized allocation system (ClinPhone, Perceptive Informatics, Deerfield, IL) to receive either HP-HMB or placebo twice daily during hospitalization and 90 days postdischarge. After eligibility criteria were ascertained, treatment assignments were obtained by the site using an interactive voice response system; no randomization envelopes were sent to the sites. Randomization was stratified by primary diagnosis, gender, and nutritional status (SGA class), with computer-generated randomization schedules using a pseudo-random permuted blocks algorithm (block sizes of 2 per strata combination).

HP-HMB was a specialized, nutrient-dense ready-to-drink liquid (Abbott Nutrition, Columbus, Ohio, USA) 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 (Abbott Nutrition, Columbus, Ohio, USA), contained 48 kcal, 12 g carbohydrate, and 10 mg vitamin C, but no other macro- or micronutrients. Products were packaged in individual single-serve Paks (237 mL), with the patients instructed to take 2 servings per day in-hospital and after discharge. The nutritional

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composition per serving of HP-HMB and placebo are shown in Supplementary Table 2. All ingredients were stable over the shelf-life of the supplements.

2.4. Outcomes

The primary efficacy variable was the composite event of death or nonelective readmission within 90 days postdischarge. Other efficacy variables included 30- and 60-day rates of readmission and/or death, length of stay (LOS), and activities of daily living (ADL) assessed using the Katz Index of Independence in Activities of Daily Living Scale [21]. This analysis also evaluated nutrition-related efficacy endpoints, including distribution of SGA nutritional status, changes in body weight at 30, 60 and 90 days postdischarge, and serum concentration of 25-hydroxyvitamin D at 30 and 60 days, which was evaluated using a central laboratory (ICON, Farmingdale, NY). Other variables will be reported separately, and a complete listing of the study outcomes is in Supplementary Table 3.

2.5. Statistical analysis

Efficacy analyses were performed using the intention-to-treat (ITT) population, defined *a priori* as all enrolled patients who received any amount of allocated intervention. For patients who prematurely discontinued study procedures and intervention, a postexit follow-up was planned to ascertain death and readmission outcomes, which were included in the ITT analysis. Missing values were not imputed in the analyses.

The sample size was calculated based on the 90-day readmission outcome. Assuming a 90-day readmission rate of 29% in the placebo group [22], and that HP-HMB would improve this rate by 10 absolute percentage points, a sample size of 228 patients per treatment was estimated to provide 80% power using a 0.05-level 1-sided log rank test. Accounting for 30% attrition, the trial needed to enroll 326 patients per group. As part of the sensitivity analysis, prior to the unblinding of the trial, the composite outcome of the competing events (90-day readmission and/or death) was redefined as the primary outcome.

For the composite outcome and its individual components, the Tarone-Ware survival (primary analysis) and unstratified Cochran–Mantel–Haenszel tests (confirmatory analysis) were used to compare HP-HMB with placebo. Post hoc analysis was performed using a stratified Cochran–Mantel–Haenszel test to ascertain the effect of imbalance in New York Heart Association (NYHA) classification. Kaplan–Meier survival curves were plotted for the primary and component outcomes. For time-to-event analyses, censoring was done at the time of the last patient contact for patients who were lost to follow-up (approximately 5% of patients in both groups). Negative binomial regression was used to analyze LOS, and generalized estimating equations for SGA. Changes from discharge in body weight were analyzed by analysis of covariance. Details of the statistical software, factors, and covariates used in the models are provided in Supplementary Table 4.

Demographics, clinical characteristics, and adverse events were compared between interventions using the Cochran–Mantel–Haenszel test for categorical variables and analysis of variance for continuous variables.

An interim analysis for the 90-day readmission was made when approximately 50% of the patients exited the study, were readmitted, or died. The Lan-Demets alpha-spending function approximating the O'Brien Fleming method was used for preserving the overall significance level at $\alpha = 0.05$. Two-sided p values were reported.

Table 1
Baseline demographic and clinical characteristics of the treatment groups.

Variable	Placebo ($n = 309$)	HP-HMB[b] ($n = 313$)
Mean age (SD), y	78.1 (8.6)	77.7 (8.2)
Male, *n* (%)	149 (48.2)	149 (47.6)
Race, *n* (%)		
Black/African-American	32 (10.4)	35 (11.2)
White	273 (88.3)	267 (85.3)
Other	4 (1.3)	11 (3.5)
Mean body weight (SD), kg	66.2 (16.0)	67.5 (17.4)
Mean BMI (SD), kg/m^2	23.9 (5.0)	24.3 (5.2)
SGA category, *n* (%)		
B, Mildly-moderately malnourished	268 (86.7)	275 (87.9)
C, Severely malnourished	41 (13.3)	38 (12.1)
Primary admission diagnosis, *n* (%)		
Heart failure	78 (25.3)	79 (25.2)
Acute myocardial infarction	25 (8.1)	30 (9.6)
Pneumonia	100 (32.5)	95 (30.4)
Chronic obstructive pulmonary disease	105 (34.1)	109 (34.8)
Mean Charlson Comorbidity Score (SD)	2.05 (1.46)	2.12 (1.48)
Government sponsored insurance, *n* (%)	276 (89)	278 (89)
Income < $25,000/y, *n* (%)	130 (42)	154 (49)
Katz ADL total score	6 (5, 6)[a]	6 (5, 6)

ADL, activities of daily living; BMI, body mass index; HP-HMB, high-protein beta-hydroxy-beta-methylbutyrate; SD, standard deviation; SGA, Subjective Global Assessment.
[a] Median (Q_1, Q_3), Q_1 is the first quartile, Q_3 is the third quartile.
[b] No significant differences were observed between treatment groups for any of the variables.

3. Results

3.1. Patients

A total of 652 patients were enrolled from 78 sites (328 HP-HMB and 324 placebo), of whom 313 and 309 received their allocated intervention, respectively, and are included in the ITT population (Fig. 1B). Among the 121 patients in HP-HMB (38.7%) and 126 in placebo (40.8%) who exited the study prior to the 90-day visit, the most common reason for discontinuation was patient's request, 66 in HP-HMB and 61 in placebo. A postexit follow-up for those who did not have a readmission before exit was conducted in 83 HP-HMB and 79 placebo patients to ascertain death and readmission outcomes; a total of 37 patients were completely lost to follow-up. Overall, clinical outcomes were unavailable from 18 and 19 patients

Table 2
Condition severity.

Severity classification	Placebo ($n = 309$)	HP-HMB ($n = 313$)
NYHA Classification among patients with heart failure, *n* (%)[a]		
Class I	4 (5.3)	1 (1.3)
Class II	27 (36.0)	46 (59.7)
Class III	31 (41.3)	25 (32.5)
Class IV	13 (17.3)	5 (6.5)
Gold Criteria for severity of chronic obstructive pulmonary disease, *n* (%)		
Stage I	3 (2.9)	3 (2.8)
Stage II	17 (16.2)	28 (25.7)
Stage III	7 (6.7)	12 (11.0)
Stage IV	9 (8.6)	9 (8.3)
Unknown	69 (65.7)	57 (52.3)
Pneumonia CRB-65 Severity Score, *n* (%)		
1	62 (62.0)	66 (69.5)
2	29 (29.0)	26 (27.4)
3	8 (8.0)	3 (3.2)
4	1 (1.0)	0

CRB-65, Confusion—respiratory rate—blood pressure for those ≥65 years of age; HP-HMB, high-protein beta-hydroxy-beta-methylbutyrate; NYHA, New York Heart Association.
[a] $p = 0.0126$ comparing distribution between treatment groups.

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in HP-HMB and placebo, respectively. Demographic characteristics were comparable between groups (Tables 1 and 2), except NYHA classification.

3.2. Treatment adherence

No difference between groups in overall product intake (Supplementary Fig. 1) was observed; during the 90-day study period, approximately one third of patients in both groups reported adherence ≥75%, and approximately 45% of patients had intake ≤25%. However, median adherence at 10 and 30 days postdischarge was relatively high, 95% and 90%, respectively in both groups. The average in-hospital intake was comparable in the 2 groups, as was the intake during the first 10 and 30 days or to the first event (readmission or death) during these periods (Supplementary Table 5).

3.3. Composite and component efficacy endpoints

There was no significant difference between groups for the primary composite endpoint (Fig. 2A). Combined nonelective readmission and mortality occurred in 84 HP-HMB patients (26.8%) and 96 placebo patients (31.1%). While 79 patients in each group had only readmissions, and mortality occurred in 15 (4.8%) and 30 (9.7%) patients in HP-HMB and placebo, respectively, 10 HP-HMB and 13 placebo patients had readmissions prior to death. No significant differences were observed between groups for the 90-day readmission rate. However, the 90-day mortality rate was significantly lower with HP-HMB relative to placebo, 4.8% and 9.7% ($p = 0.018$), respectively (Fig. 2A), with a relative risk 0.49 (95% confidence interval [CI], 0.27 to 0.90). Survival analysis further showed no statistical difference in time to readmission or death between treatment groups (Fig. 2B). The time to readmission was similar between groups (Fig. 2C). The Kaplan–Meier curve for mortality (Fig. 2D) showed significantly greater survival with HP-HMB relative to placebo ($p = 0.013$). In a post hoc analysis adjusting for the imbalance of the NYHA classification, odds ratios for treatment effect were observed to be homogeneous across classes (data not shown). Additionally, post hoc estimation of the number needed to treat (NNT) to prevent 1 death (method in Supplementary Table 4) was 20.3 (95% CI, 10.9 to 121.4).

Evaluation at 30 and 60 days postdischarge (Supplementary Fig. 2) showed no significant differences between treatment for the composite variable or for readmission alone, but mortality was significantly lower in the HP-HMB group relative to placebo at 30

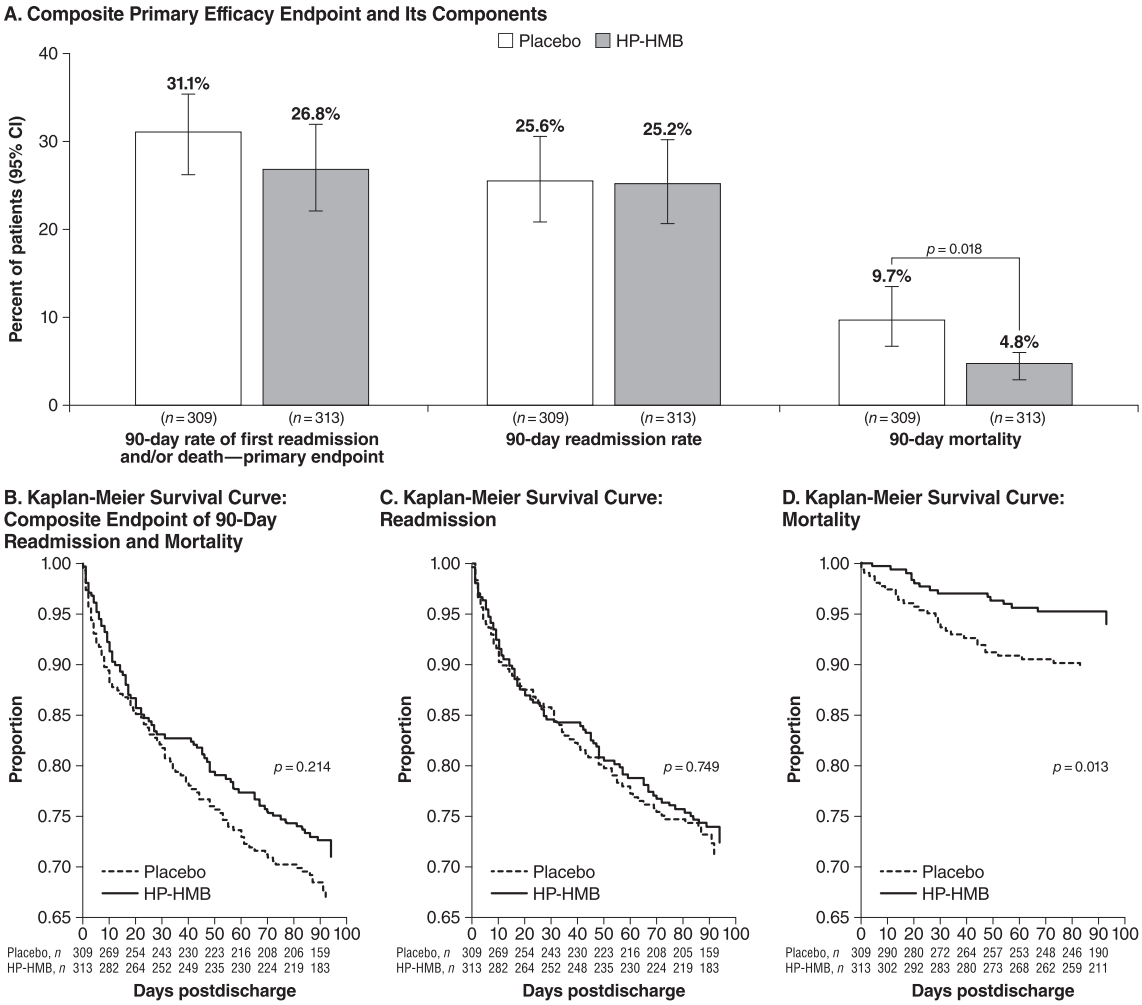

Fig. 2. Primary efficacy outcome and components (intention-to-treat population). A. No significant difference between treatment groups for the primary composite endpoint, but on the individual components, HP-HMB exhibited a significantly lower 90-day mortality rate than placebo ($p = 0.018$). B–D. Kaplan–Meier survival curves for time to death or first readmission (B), time to readmission (C) and time to death (D), which was significantly longer in the HP-HMB group ($p = 0.013$). HP-HMB, high-protein beta-hydroxy-beta-methylbutyrate.

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days (2.9% vs. 6.2%; $p = 0.049$) and 60 days postdischarge (4.2% vs. 8.7%; $p = 0.020$).

While mortality resulted from a range of causes, including cancer in 3 patients diagnosed subsequent to study enrollment, most deaths were due to cardiorespiratory conditions (Supplementary Table 6).

3.4. Other efficacy endpoints

No significant effects on mean total LOS were observed (HP-HMB, 5.0 [standard deviation (SD), 3.2] vs. placebo 5.1 [SD, 3.6]); ADL was also similar between treatments at days 30, 60, and 90 (median [1st quartile, 3rd quartile] was 6 [6, 6] for both groups). Changes were observed in nutritional status such that the proportion of patients categorized as SGA-A (well-nourished) increased over the study duration in both groups (Fig. 3A). These increases were consistently greater with HP-HMB, peaking at day 90, with 45.5% of these patients classified as SGA-A compared with 30.0% in the placebo group. The differences in SGA levels between groups at day 90 resulted in significantly higher odds of patients in the HP-HMB group achieving a better nutritional status relative to placebo (odds ratio = 2.04, 95% CI, 1.28 to 3.25; $p = 0.009$).

At day 30, body weight was improved by least squares mean (standard error [SE]) of 0.55 (SE, 0.32) kg in HP-HMB group, but decreased by 0.26 (SE, 0.34) kg from discharge in placebo, with a difference showing significance ($p = 0.035$; Fig. 3B). Although not statistically different, changes in body weight were consistently higher in HP-HMB group at days 60 and 90 (Fig. 3B). Serum levels of 25-hydroxyvitamin D (Fig. 4) were significantly higher with HP-HMB than placebo at days 30 and 60 ($p = 0.035$ and $p = 0.008$, respectively).

3.5. Safety

A comparable proportion of patients in both groups reported treatment-emergent adverse events (serious plus nonserious

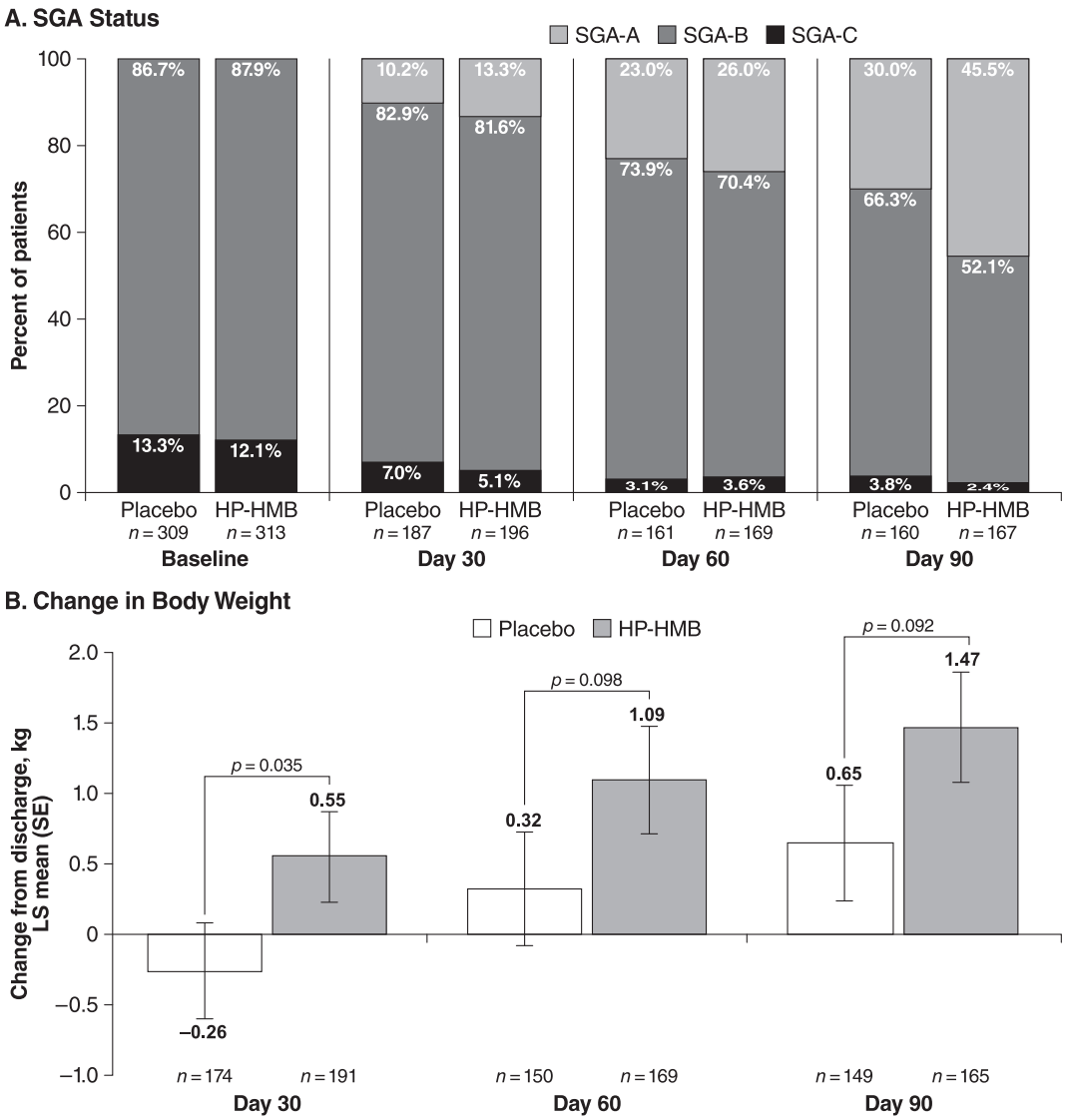

Fig. 3. Nutritional status and weight change. While consistent improvements in nutritional status, as determined by the SGA scores, were observed over the study duration in both treatment groups (A), the specialized, nutrient-dense oral nutritional supplement, HP-HMB, resulted in significantly higher odds of patients achieving a better nutritional status at day 90 relative to the placebo group (odds ratio = 2.04, 95% CI = 1.28 to 3.25, $p = 0.009$). The differences between treatments in body weight change from discharge significantly favored HP-HMB at day 30 (B). CI, confidence interval; HP-HMB, high-protein beta-hydroxy-beta-methylbutyrate; LS, least squares; SE, standard error; SGA, Subjective Global Assessment.

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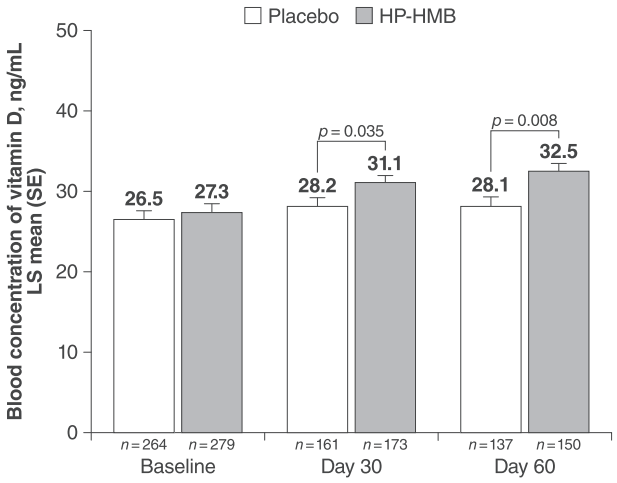

Fig. 4. Serum concentrations of 25-hydroxyvitamin D. HP-HMB, high-protein beta-hydroxy-beta-methylbutyrate; LS, least squares; SE, standard error.

adverse events; 44% in the placebo group and 47% in the HP-HMB group, respectively (Table 3). In addition, study discontinuation due to adverse events was not different between groups (12% placebo, 11% HP-HMB). The most common adverse events (occurring in ≥5% of patients) were exacerbations of COPD, constipation, and diarrhea (Table 3).

4. Discussion

Despite efforts in preventing and treating malnutrition, the prevalence of disease-related malnutrition remains consistently high [1]. The NOURISH study represents the largest randomized controlled trial to date evaluating the effects of adding a specialized nutrient-dense ONS therapy to standard of care on hospital readmission and mortality in an older population hospitalized for CHF, AMI, PNA, and COPD. In addition to incorporating a rigorous intention-to-treat study design, in contrast to many of the previous studies included in meta-analyses [11–13], the patients were specifically required to show evidence of malnutrition at entry, as indicated by inclusion criteria of SGA classes of B or C.

The primary composite endpoint was not achieved, and no differences were observed with regard to readmission rates. This lack of a difference in the readmission is in contrast to other studies showing a reduction in readmission among patients treated with ONS [13,14] and may be due to a variety of factors such as the heterogeneity of the study population, length of follow-up, nutritional treatment modality, and possibly the competing events of readmission and mortality. In the present study, the higher mortality in the placebo group may have contributed to the similar hospital readmission rates in the 2 groups, since some patients died without a readmission. The heterogeneity of patients with respect to the included diagnoses and exclusion of patients with high-risk conditions such as cancer, diabetes, and chronic renal failure may also have contributed to the lack of significance for the composite and readmission outcomes.

Initiation of HP-HMB during hospitalization and continuation postdischarge resulted in a significantly lower mortality rate. At each of the evaluated time points of 30, 60, and 90 days postdischarge, there was a consistent reduction in mortality. This is in accord with evidence suggesting that ONS intervention is associated with reduced mortality; a review of 32 trials reported a relative risk of 0.74 (95% CI, 0.59 to 0.92) for mortality in ONS versus control [11]. In addition, the NNT for HP-HMB was low (NNT = 20.3) suggesting that provision of HP-HMB to malnourished older adults may be an effective strategy to improve current standard nutritional care.

Adherence with study intervention was not different between treatment groups, and was similar to that of another randomized controlled trial of oral nutritional supplements in illness [22]. Adherence with intake of ONS has been reported to have a wide range (38%–100%) in various studies [23], which in the clinical setting may, in part, be dependent on appetite, other clinical variables, or on reimbursement policies. Adherence with ONS is challenging, even over a short period of intervention. In one 28-day study, 40% of patients had less than one quarter of intended consumption, 9% had 25%–50%, 16% had 50%–75%, and 35% had more than three quarters, yet the nutritional intervention resulted in significant benefits over 6 months relative to controls, including fewer readmissions [24]. In the current study, the greater increases in body weight and serum 25-hydroxyvitamin D concentration among the HP-HMB patients relative to placebo can be considered indicative of adherence with product intake, although such increases are also likely to indicate nutritional benefits.

The HP-HMB was unique in that, in addition to providing the known essential macro- and micronutrients, it had a high protein composition and was further supplemented with HMB. Both protein and HMB supplementation have individually been shown to improve protein accretion and attenuate LBM loss [18,25], the latter of which is an independent predictor of mortality in older adults [26]. Additionally, HMB may help prevent muscle protein degradation during catabolic illness [27]. Increases in LBM and body weight resulting from ONS therapy, with concomitant increases in clinically relevant functional indices, have been especially noted in patients with COPD [28]. Additionally, in patients with COPD, body weight is an independent predictor of mortality, and in some patients, negative effects of low body weight may be reversed with nutritional therapy [29].

This study may have limited generalizability, since it represents a selected initially hospitalized population, albeit for common medical conditions that are considered the leading diagnoses contributing to postdischarge readmissions in older adults [19,20]. Further, the current study was not designed to determine the effect of individual nutrients, thus the specific components in HP-HMB that may be responsible for the reduced mortality could not be determined. While lack of dietary intake data other than for HP-HMB is a study limitation, the significant differences in mortality may suggest that there are

Table 3
Treatment-emergent adverse events.[a]

Event	Placebo (n = 309)	HP-HMB[c] (n = 313)
	Patients, n (%)	
Adverse events[b]	136 (44)	146 (47)
Serious adverse events	92 (30)	82 (26)
Study discontinuation owing to an adverse event[b]	37 (12)	33 (11)
Most common serious adverse events		
Chronic obstructive pulmonary disease exacerbation	23 (7)	18 (6)
Most common nonserious adverse events		
Constipation	9 (3)	15 (5)
Diarrhea	17 (6)	18 (6)

HP-HMB, high-protein beta-hydroxy-beta-methylbutyrate.

[a] Serious and nonserious adverse events were categorized by the *Medical Dictionary for Regulatory Activities*. Only events that occurred in at least 5% of patients in either study group are summarized.

[b] Serious and nonserious adverse events.

[c] No significant differences were observed between treatment groups for any of the treatment-emergent adverse events.

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clinical benefits of HP-HMB regardless of a potential effect of other dietary intake. The current body of evidence suggests that providing patients with ONS does not reduce dietary intake [30]. The difficulty in blinding nutritional studies may also be a limitation, but several strategies were used to maintain the double-blind, and there was no indication that this blind was broken.

5. Conclusion

This double-blind, ITT, randomized, placebo-controlled study showed that a specialized, nutrient-dense ONS containing high protein and HMB did not alter the primary composite endpoint of hospital readmission rates and mortality in this specific population of malnourished, older adults hospitalized for CHF, AMI, PNA, or COPD. However, early administration (within 72 h of hospitalization) of HP-HMB in addition to the current nutritional care was associated with decreased postdischarge mortality and improved nutritional status. Further analyses are required to understand the mechanism(s) leading to these observed effects.

Author contributions

Conception and design: EMM, ML, GEB, JLN, RAH. Analysis and interpretation of data: NED, EMM, LEM, ML, GEB, JLN, RAH, KAT, TRZ. Drafting of the article: NED, EMM, ML, GEB, JLN, RAH, TRZ. Critical revision for important intellectual content: NED, EMM, LEM, ML, GEB, JLN, RAH, KAT, TRZ.

Final approval of the article: NED, EMM, LEM, ML, GEB, JLN, RAH, KAT, TRZ.

Provision of study material or patients: NED, EMM, LEM, ML, GEB, JLN, RAH, TRZ.

Statistical expertise: EMM, ML, GEB, JLN, RAH. Administrative, technical, or logistic support: NED, EMM, LEM, ML, GEB, JLN, RAH, KAT, TRZ. Collection and assembly of data: NED, EMM, LEM, TRZ collected data. ML, GEB, JLN, RAH provided insight on data assembly.

Conflict of interest

NED and LEM report receiving grant funding and consulting fees from Abbott Nutrition. EMM reports receiving grant funding from Abbott Nutrition; he and the Medical University of South Carolina received consulting fees from Abbott Nutrition. GEB, JLN, and ML report employment, including stock ownership/options and pending patents, by Abbott Nutrition. RAH reports employment, including stock ownership/options, by Abbott Nutrition. KAT reports receiving grant funding, consulting fees, and honoraria from Abbott Nutrition. TRZ reports receiving grant funding and consulting fees from Abbott, Inc., and has served as Emory University site principal investigator for a multicenter tube feeding trial sponsored and initiated by Nestlé Inc.

Role of the funding source

This study was supported by Abbott Nutrition. The protocol was developed by the sponsor (Abbott Nutrition) in consultation with independent experts. Data were collected by the investigators and analyzed by the sponsor and subsequently reviewed by an independent statistician. All study investigators had confidentiality agreements with the sponsor. All authors take responsibility for the accuracy and completeness of the data, statistical analyses, and compliance of the study with the protocol.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2015.12.010.

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