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Supplementation with Selenium and Coenzyme Q10 Reverses and Prevents Renal Shrunken Pore Syndrome and Reduces All-Cause and Cardiovascular Mortality: Sub-Analysis of an RCT in Elderly Adults with Low Selenium Status

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Abstract

Shrunken pore syndrome (SPS), defined as an eGFR cystatin C/eGFR creatinine ratio (eGFR ratio) ≤ 0.7, has been associated with increased morbidity and mortality. This study investigated the ratio's predictive value for cardiovascular (CV) and all-cause mortality in an elderly, selenium-deficient population and assessed the effects of combined selenium (200 µg/day) and coenzyme Q10 (CoQ10; 200 mg/day) supplementation on SPS prevalence, progression, and mortality. In this exploratory sub-study, 283 participants (mean age 77 years) were randomized to supplementation or placebo and followed for 12 years, with SPS prevalence assessed at baseline and after 48 months. SPS was associated with increased all-cause ($p = 0.015$) and CV mortality ($p = 0.016$). Plasma GPx3 activity correlated with the eGFR ratio, while low SELENOP (<3.23 mg/L) or selenium (<70 µg/L) predicted higher mortality among placebo recipients. After 48 months, SPS prevalence and the eGFR ratio improved with supplementation but worsened with placebo. Among participants with SPS, supplementation was associated with an improved eGFR ratio ($p = 0.007$) and lower all-cause (HR 0.36; 95% CI 0.16–0.86) and CV mortality (HR 0.25; 95% CI 0.08–0.75). Despite the limited sample size, these findings support the eGFR ratio as a prognostic marker and suggest that selenium and CoQ10 supplementation may reduce SPS prevalence and progression and improve long-term survival.

Keywords: shrunken pore syndrome (SPS); eGFR ratio; selenium and CoQ10 supplementation; cardiovascular mortality; elderly population

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1. Introduction

Renal function is central to systemic homeostasis, and subtle changes in glomerular filtration rate (GFR) can have profound effects on multiple organ systems. In clinical practice, GFR is estimated using equations based on creatinine (molecular weight 113.1 Da) or cystatin C (molecular weight ≈13.4 kDa) in plasma or serum. The glomerular filtration of these compounds is similar, and hence, estimates of GFR based on creatinine (eGFRcreatinine) and cystatin C (eGFRcystatin C) normally agree [1]. Patients for whom eGFRcystatin

C is significantly lower than eGFRcreatinine, without extra-renal factors influencing the estimates, seem to suffer from a particularly serious group of conditions called 'selective glomerular hypofiltration syndrome', which includes 'shrunken pore syndrome' (SPS). The syndrome was identified by a low eGFRcystatin C/eGFRcreatinine ratio (eGFRcyst./creat. ratio) [2]; later, however, a negative difference between eGFRcystatin C and eGFRcreatinine was also used to identify the syndrome [3–6]. Patients with SPS show a higher mortality and cardiovascular disease risk than patients for whom eGFRcystatin C and eGFRcreatinine agree [2–4,7–10]. The syndrome is characterized by reduced filtration and increased retention of plasma proteins of 5–30 kDa, including cystatin C and other atherogenic serum proteins [11]. Even for patients with measured GFR within the reference range (>60 mL/min/1.73 m^2) but with eGFRcystatin C significantly lower than eGFRcreatinine, higher mortality is observed than for patients with concordant estimates [5–7,9,12]. In previous research, the syndrome was identified by a low eGFRcystatin C/eGFRcreatinine ratio [2], but a negative difference between eGFRcystatin C and eGFRcreatinine has subsequently also been used to identify the syndrome [3–6]. The mortality of patients displaying the syndrome appears to be inversely associated with the eGFRcystatin C/eGFR creatinine ratio [2–9]; however, so far, no treatment increasing the ratio with a consequent reduced mortality has been identified.

Selenium is an essential trace element incorporated as selenocysteine into selenoproteins, which are encoded by 25 separate genes in humans [13–15]. Owing to its dissociation at physiological pH and high nucleophilicity, the selenol group of selenocysteine plays a critical role in selenoenzymes, which contribute to antioxidant defense, redox regulation, thyroid hormone control, and prevention of protein misfolding [16,17]. Selenium availability varies markedly with soil content, leading to substantial regional differences in dietary intake. Mainland Europe and Scandinavia are characterized by low selenium intake, whereas intake levels in the United States are generally higher [18,19]. Low selenium status has been associated with impaired antioxidant capacity, thyroid dysfunction, increased inflammation, and a higher risk of cardiovascular and renal disease [20–26].

Selenoprotein P (SELENOP) is a circulating glycoprotein containing up to 10 selenocysteine residues and is primarily synthesized and secreted by the liver. It plays a central role in the systemic transport of selenium to peripheral tissues, including the thyroid, brain, heart, kidneys, and testes [27]. In the circulation, SELENOP represents the major extracellular selenoprotein and accounts for approximately 60–70% of total serum selenium in selenium-replete individuals [14,28]. Circulating concentrations of SELENOP are strongly associated with selenium intake; consequently, SELENOP is widely regarded as a reliable indicator of the bioavailable selenium fraction in blood and is considered one of the most informative biomarkers of selenium status in clinical studies [14,29,30].

Coenzyme-Q10 (CoQ10) is an essential component of the mitochondrial electron transport chain and is a lipid-soluble antioxidant whose endogenous levels decline with age [31]. Its antioxidant function depends on reducing equivalents provided by the Ferroptosis Suppressor Protein 1 (FSP1) [32,33] and the selenoenzyme thioredoxin reductase 1, and it works in concert with the selenoenzyme glutathione peroxidase 4 against lipid peroxidation, indicating that a functional interdependence exists between selenium and CoQ10.

Glutathione peroxidase 3 (GPx3) is a secreted extracellular selenoprotein that reduces hydrogen peroxide and lipid hydroperoxides and is primarily of renal origin [34–40]. GPx3 is found in the renal cortex in parietal cells of Bowman's capsule, but mainly in the basement membrane of proximal tubular cells, from which it is secreted into plasma.

Circulating GPx3 activity reflects both selenium status and renal function, as it is reduced in chronic and acute renal failure and correlates inversely with disease severity [39,41,42].

Previously, in an elderly Swedish population with low selenium status, we found that impaired renal function was associated with low selenium levels. In the same cohort, a randomized, double-blind, placebo-controlled trial demonstrated that combined supplementation with selenium and CoQ10, along with increasing GPx3, significantly improved renal function, assessed by estimated glomerular filtration rate (eGFR) using the CKD-EPI algorithm [26,43].

The present study is a follow-up of the former main study [44], with a two-fold aim: first, to investigate whether SPS, i.e., a reduced ratio of cystatin C- and creatinine-derived eGFR, is associated with cardiovascular (CV) or all-cause mortality and second, to evaluate whether long-term supplementation with selenium and CoQ10 influences the prevalence and progression of SPS. This exploratory sub-study of the previously published KiSel-10 trial investigated whether SPS predicts all-cause and cardiovascular mortality and whether selenium plus CoQ10 supplementation influences SPS prevalence and progression.

2. Materials and Methods

2.1. Study Subjects

All individuals aged 69–88 years ($n = 1320$) living in a defined municipality in southeast Sweden were invited to participate in an epidemiological project. Of these, 876 agreed to participate and underwent baseline clinical examination and blood sampling. In a subsequent intervention study, participants were randomized to receive selenium and CoQ10 supplementation or placebo for 48 months. The first participant was included in January 2003, and the last participant concluded the study in February 2010.

The participants received daily dietary supplements of 200 mg of CoQ10 in capsule form (Bio-Quinon 100 mg B.I.D., Pharma Nord, Vejle, Denmark) and 200 µg of organic selenium yeast tablets (SelenoPrecise 100 µg B.I.D., Pharma Nord, Vejle, Denmark) ($n = 221$), or a similar placebo ($n = 222$) over 48 months. This supplementation was given in addition to any regular medications they were taking. To measure compliance, all unused study medications (both active and placebo) were returned and counted, with no significant difference in unused medications between the two groups. The final population in the present sub-study consisted of 283 participants, divided into supplementation and placebo groups. The study subjects were followed for 12 years using data from the Swedish death register, and cardiovascular and all-cause mortality were calculated for the two groups separately. Selection was based on the availability of complete baseline creatinine and cystatin C measurements required for eGFR ratio calculations. Possible selection bias is discussed in the limitations.

2.2. Ethical Approval

The study was approved by the Regional Ethics Committee (Forskningsetikkommittén, Hälsouniversitetet, SE-581 85 Linköping, Sweden; approval no. D03-176; approval date 6 May 2003) and was conducted in accordance with the ethical principles of the Declaration of Helsinki (1975). Review by the Medical Products Agency was not required, as the study did not involve the investigation of a medicinal product for a specific disease but focused on commercially available food supplements. The trial was registered at ClinicalTrials.gov (identifier: NCT01443780; registration date 28 September 2011). Registration was completed retrospectively, as prospective registration was not mandatory at the time of study initiation. Written informed consent was obtained from all participants prior to enrolment.

2.3. Blood Sampling

Blood samples were collected at baseline and after 48 months, with participants resting in a supine position. Plasma and serum were processed under standardized conditions

and stored at −70 °C until analysis. Samples were stored as aliquots and thawed twice, the second time for the present analyses. Long-term storage may have introduced analytical variability and is acknowledged as a limitation.

2.4. Determination of Selenium

The serum selenium analyses were performed using ICP-MS methodology on an Agilent 700 platform at Kompetenzzentrum für komplementärmedizinische Diagnostik, Zweigniederlassung der synlab MVZ Leinfelden GmbH (Leinfelden-Echterdingen, Germany). The accuracy of the measurements was checked by analyzing two external reference materials with certified values of 63 µg/L and 103 µg/L (control program offered by the Society for Advancement of Quality Assurance in Medical Laboratories, INSTAND e.V., Düsseldorf, Germany), showing values within 90–110% of certified concentrations. The precision of the method, checked by repetitive analyses of the same sera, showed an average coefficient of variation of 5.7%.

2.5. Determination of Creatinine and Cystatin C

Serum creatinine was measured using an enzymatic method calibrated against isotope-dilution mass spectrometry. Cystatin C was determined using a particle-enhanced turbidimetric immunoassay calibrated against the international calibrator ERM-DA471/IFCC [45]. Both assays were performed on a standardized chemistry analyzer with internal and external quality controls.

2.6. Estimation of Renal Function and Shrunken Pore Syndrome

Estimated GFR (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations [46]:

- eGFRCreatinine: CKD-EPI creatinine equation (2009).
- eGFRCystatin C: CKD-EPI cystatin C equation (2012).

The SPS was defined according to the eGFR ratio:

$$\text{eGFR ratio} = \text{eGFRcystatin C}/\text{eGFRcreatinine}$$

We considered an eGFR ratio ≤ 0.7 as indicative of SPS, based on prior literature suggesting clinically relevant discordance thresholds [47,48]. In some analyses, due to relatively few individuals with ratio ≤ 0.7, we also used a cut-off of ≤ 0.9. The ratio was also used as a continuous variable. The ≤ 0.9 threshold was used in supplementary analyses to increase statistical power for Cox regression analyses but represents a broader phenotype than classical SPS.

2.7. Quantification of Selenoprotein P (SELENOP)

SELENOP concentrations were determined using the selenOtest ELISA (selenOmed GmbH, Berlin, Germany), a chromogenic enzyme-linked immunosorbent assay specific for human SELENOP (lot STE.21002). Calibrators and quality control samples were included in duplicate on each assay plate to ensure standardization and to monitor assay performance. Serum samples were diluted 1:40 and processed according to the manufacturer's instructions. Concentrations were calculated using a four-parameter logistic (4PL) regression model based on a logarithmic standard curve. Inter-assay and intra-assay coefficients of variation, calculated from the control samples, were below 5% throughout the analyses. During establishment of the assay, freeze–thaw cycles of serum samples were tested for a potential effect on SELENOP concentration analysis, and the results remained unaffected, with a variation of less than 20% after up to five cycles.

2.8. Determination of GPx3

Extracellular GPx3 activity was determined in the serum samples, as previously described, by a coupled enzymatic test monitoring NADPH consumption at 340 nm. Its decline is due to the coupled reaction, in which glutathione reductase regenerates glutathione that has been oxidized by GPx3 activity to reduce the added H_2O_2 substrate [48]. The reactions were initiated by adding H_2O_2 to the reaction buffer containing reduced glutathione, NADPH, and glutathione reductase along with serum samples, each of 5 µL. NADPH decline was detected spectroscopically in the 96-well plates and converted to units of enzymatic activity as described. A serum control sample was included in each assay run to assess the analytical quality, yielding inter- and intra-assay CVs of less than 15% during the analysis [49].

2.9. Clinical Examinations

The participants were assessed by one of three experienced cardiologists, who performed a standardized clinical evaluation, including blood pressure measurement, New York Heart Association functional class assessment, electrocardiogram (ECG), and echocardiography. Left ventricular systolic ejection fraction (EF) was categorized into four classes (<30%, 30–39%, 40–49%, ≥50%).

2.10. Statistical Methods

Descriptive statistics were presented as mean ± standard deviation (SD) or percentages. Group differences were analyzed using Student's *t*-test for continuous variables and the chi-square test for categorical variables. Pearson correlation and multiple regression analyses were performed to evaluate associations between eGFR and clinical covariates. Normality and variance assumptions were evaluated. Welch tests produced similar results and did not alter the conclusions.

In the intervention sub-study, repeated measures of variance were used to obtain specific information on the individual changes in the concentration of the biomarkers analyzed, compared to group mean values. To evaluate the effect size of the intervention, we used Cohen's d.

Kaplan–Meier and Cox proportional hazards regression analyses were used to evaluate the risk of CV mortality during the follow-up period. The independent variables included in the multivariate model were known to be associated with all-cause and CV mortality. They were age, smoking, diabetes, hypertension, ischemic heart disease (IHD), selenium level, EF < 40%, and active treatment. However, as the size of the SPS population was small, to avoid overadjustment bias, we chose only to include diabetes and IHD as covariates in those Cox regressions. In the calculation to evaluate the increased risk of having low selenium/SELENOP concentrations, the covariates chosen were hypertension, diabetes, IHD and selenium < 70 µg/L, or SELENOP < 3.23 mg/L.

A p value < 0.05 was considered statistically significant. Analyses were performed using Statistica v.13.2 (Dell Inc., Tulsa, OK, USA).

3. Results

3.1. Study Population

This is an exploratory sub-study based on the main study including 443 elderly participants, where half were supplemented with selenium and coenzyme Q10 combined, while the other half received a placebo, and where active treatment reduced cardiovascular mortality, increased cardiac function, and decreased cardiac wall stress (Figure 1) [44].

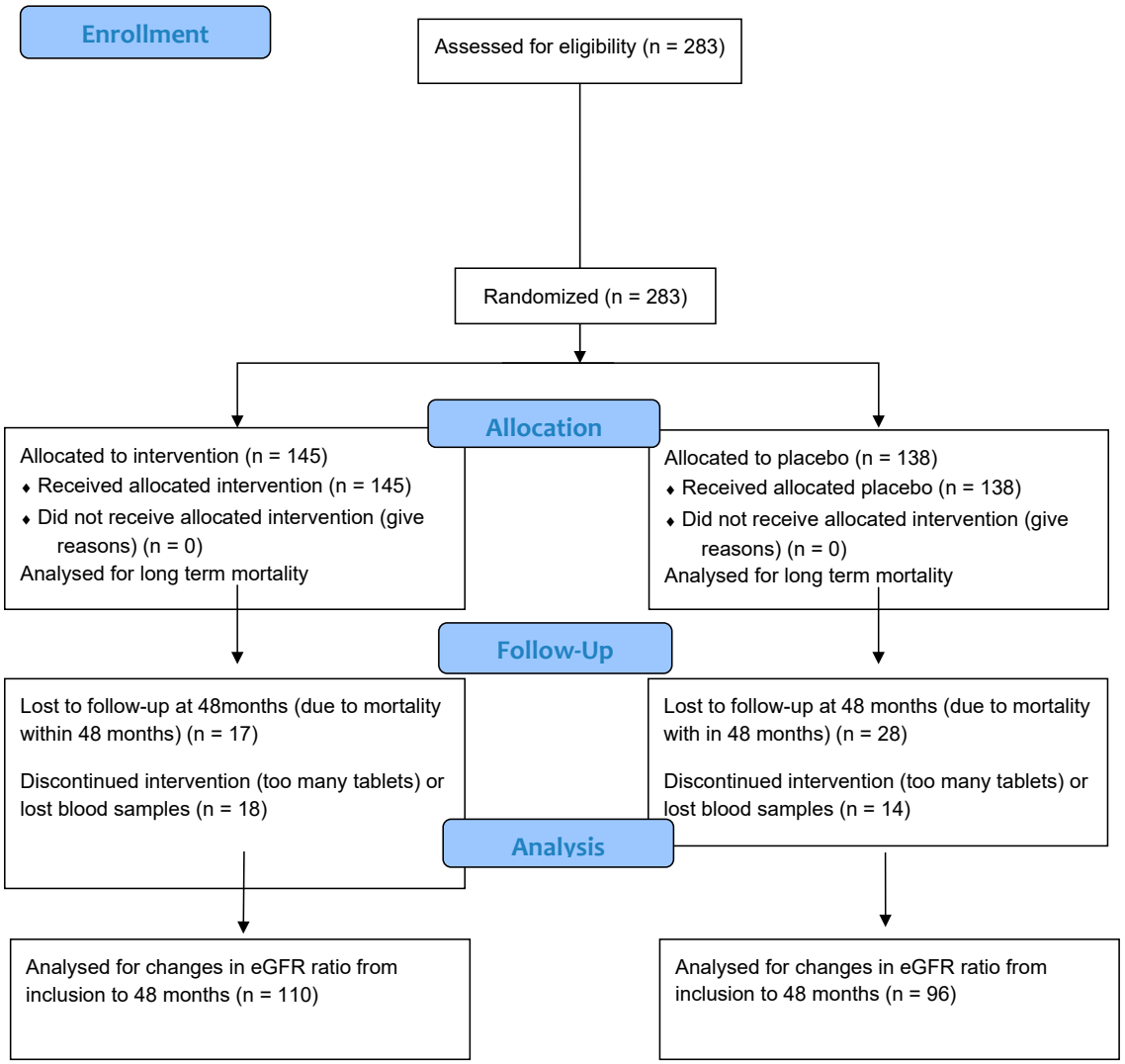


Figure 1. CONSORT flow diagram.

The present sub-study included a total of 283 participants, of whom 145 were assigned to the active treatment group and 138 to the placebo group. Within the study population, 205 participants (72.4%) had hypertension, 57 (20.1%) had diabetes mellitus, 65 (23.0%) had IHD, and 22 (7.8%) had impaired cardiac function with EF < 40% (Table 1). The prevalence of comorbid conditions was consistent with that expected in a population of elderly, community-dwelling individuals. Baseline characteristics were comparable between the two randomized groups, with no statistically significant differences observed in any baseline variables (Table 1).

The 48-month prevalence calculations are based on survivors with available blood samples.

Table 1. Baseline characteristics of the study population receiving active treatment or placebo during an intervention time of four years.

Variables	Active	Placebo	*p* Value
n	145	138	
Age years mean (SD)	76.9 (3.4)	77.0 (3.5)	0.88
Males/Females *n*	81/64	70/68	
History			
Smokers, present *n* (%)	18 (12.4)	14 (10.1)	0.55
Diabetes *n* (%)	28 (19.3)	29 (21.0)	0.72
Hypertension *n* (%)	101 (69.7)	104 (75.4)	0.28
IHD *n* (%)	33 (22.8)	32 (23.2)	0.93
Medications			
ACEI/ARB *n* (%)	28 (22.8)	32 (23.2)	0.43
Beta-blockers *n* (%)	53 (36.6)	49 (35.5)	0.85
Diuretics *n* (%)	48 (33.1)	48 (34.8)	0.77
Examinations			
EF < 40% *n* (%)	12 (8.3)	10 (7.3)	0.75
s-selenium µg/L, mean (SD)	65.5 (16.7)	67.5 (13.8)	0.57

Note: ACEI: ACE inhibitors; ARB: Angiotensin receptor blockers; EF: Ejection fraction; IHD: Ischemic heart disease; SD: Standard deviation. Note: Values are means ± SD or frequency (percent). Note: Student's unpaired two-sided *t*-test was used for continuous variables, and the chi-square test was used for analysis of one discrete variable.

3.2. All-Cause and CV Mortality and Comorbid Conditions and Exposures for Individuals with eGFR Ratio <0.7 vs. >0.7 Within a Follow-Up Period of 12 Years

The number of participants surviving 12 years from study entry was lower in the ≤0.7 group than in the >0.7 group (Z = 2.43; $p = 0.015$) (Figure 2).

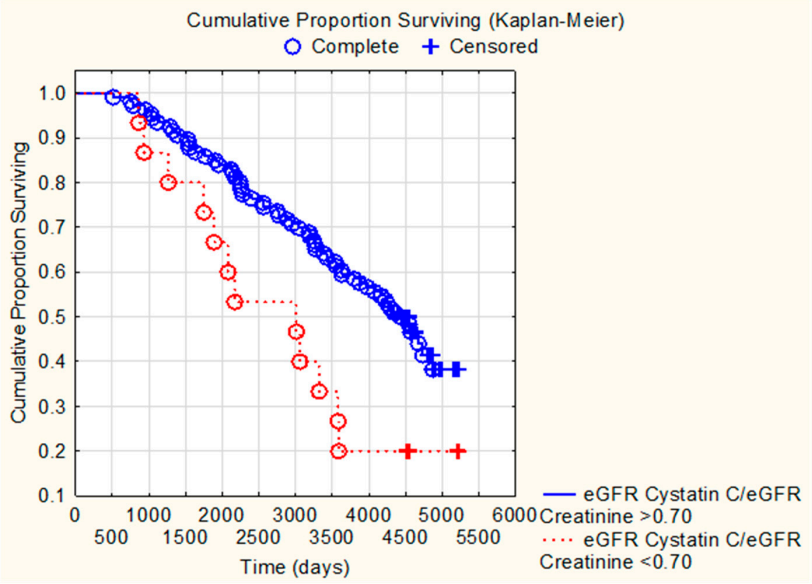


Figure 2. Kaplan–Meier graph illustrating survival from all-cause mortality in the total population stratified according to an eGFRCystatin C/eGFRCreatinine ratio of ≤0.7 versus >0.7 within a follow-up period of 12 years. Note: Z = 2.43, $p = 0.015$.

The corresponding numbers and rates of CV mortality were also significantly lower in the >0.70 group ($Z = 2.40$; $p = 0.016$) (Figure 3). Thus, we observed higher all-cause and CV mortality in those with SPS compared with those without the syndrome.

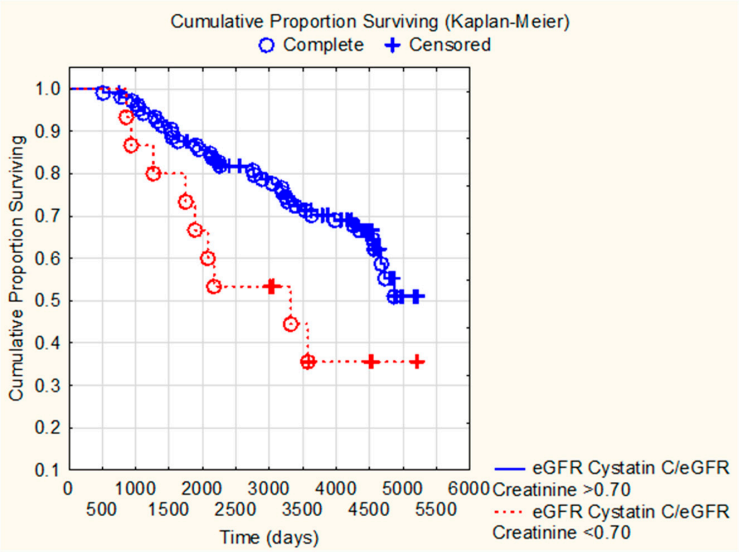


Figure 3. Kaplan–Meier graph illustrating survival from CV mortality in the total population stratified according to an eGFRCystatin C/eGFRCreatinine ratio of ≤0.7 versus >0.7 within a follow-up period of 12 years. Note: $Z = 2.40$; $p = 0.016$.

We further investigated whether the two groups differed at baseline with respect to age, comorbid conditions, and factors other than SPS that might impact the mortality of the two groups (Table 2).

Table 2. Distribution of baseline characteristics of the study population divided into SPS (eGFR ratio ≤ 0.7), non-SPS (eGFR ratio > 0.7), eGFR ratio ≤ 0.9, and eGFR ratio > 0.9.

Variables	SPS	Non-SPS	*p* Value	eGFR ≤ 0.9	eGFR > 0.9	*p* Value
n	32	225		125	132	
Age years mean (SD)	77.2 (3.9)	76.6 (3.3)		76.7 (3.5)	76.7 (3.2)	
History						
Smoker, *n* (%)	4 (12.5)	23 (10.2)	0.69	14 (11.2)	13 (9.9)	0.72
Diabetes, *n* (%)	4 (12.5)	45 (20.0)	0.31	24 (19.2)	25 (18.9)	0.96
Hypertension, *n* (%)	23 (71.9)	165 (73.3)	0.86	89 (71.2)	99 (75.0)	0.49
IHD, *n* (%)	8 (25.0)	46 (20.4)	0.55	28 (22.4)	26 (19.7)	0.60
AF, *n* (%)	4 (12.5)	24 (10.7)	0.76	12 (9.6)	16 (12.1)	0.52
Medication						
ACEI/ARB, *n* (%)	8 (25.0)	45 (20.0)	0.32	30 (24.0)	23 (17.4)	0.19
Beta-blockers, *n* (%)	14 (43.8)	78 (34.7)	0.32	51 (40.8)	41 (31.1)	0.10
Diuretics, *n* (%)	16 (50.0)	73 (32.4)	0.051	45 (36.0)	44 (33.3)	0.65
Examinations						
EF < 40%, *n* (%)	2 (6.3)	15 (6.7)	0.93	8 (6.4)	9 (6.8)	0.89
s-selenium incl, µg/L mean (SD)	65.4 (17.7)	64.0 (17.4)	0.70	62.9 (18.0)	65.0 (16.8)	0.35
Lost blood samples, *n*	-	26		9	17	

Note: ARB: Angiotensin II receptor blockers; ACEI: Angiotensin-converting enzyme receptor blockers; AF: Atrial fibrillation; EF: Ejection fraction; IHD: Ischemic heart disease.

We also included information on the groups obtained after using a cut-off of 0.9, which was used in analyses of the impact of baseline selenium and which yielded similarly sized groups for comparison. No significant differences in characteristics at baseline were found between the latter groups.

3.3. Level of Selenium and Mortality Risk in Those with Low eGFR Ratio

We conducted a Cox proportional hazards regression analysis to examine the influence of selenium level on the risk of all-cause and CV mortality within 12 years. We selected individuals from the placebo group, but due to the small sample size, we chose a cut-off level of the eGFR ratio of <0.9 to increase and harmonize the sample size and to allow more covariates to be included in the model (Tables 3 and 4). Notably, the increased CV mortality risk appears to start at around this less severe eGFR ratio [49].

Table 3. Cox proportional hazards regression analysis evaluating risk of all-cause mortality after 12 years in those (among the placebo group) with an eGFRcystatin C/eGFRcreatinine ratio ≤ 0.9 (and without any active intervention).

Variables	Beta Value	Hazard Ratio	T-Value	95% CI	*p* Value
Hypertension	−0.42	0.66	−1.09	0.31–1.40	0.27
Diabetes	0.32	1.38	0.71	0.57–3.32	0.48
Ischemic heart disease	0.78	2.18	1.98	1.01–4.70	0.047
Selenium, <70 µg/L	1.28	3.60	3.27	1.67–7.76	0.001

Table 4. Cox proportional hazards regression analysis evaluating the risk of CV mortality after 12 years in those (among the placebo group) with an eGFRcystatin C/eGFRcreatinine ratio ≤ 0.9 (and without any active intervention).

Variables	Beta Value	Hazard Ratio	T-Value	95% CI	*p* Value
Hypertension	−0.35	0.71	−0.75	0.28–1.75	0.45
Diabetes	0.46	1.59	0.91	0.59–4.29	0.36
Ischemic heart disease	0.76	2.14	1.69	0.89–5.17	0.09
Selenium, <70 µg/L	0.97	2.63	2.09	1.06–6.51	0.004

The regression analyses showed that, in the untreated group, among individuals with an eGFR ratio ≤ 0.9, having a selenium concentration below 70 µg/L significantly increased both all-cause and CV mortality, compared with those having a selenium concentration above 70 µg/L, even when adjusting for some known covariates influencing the mortality risk.

To validate these results, we also examined the impact of the most important transport protein for selenium in plasma, SELENOP, in the same setup. We chose a cut-off value for SELENOP of 3.23 mg/L, which corresponds to a serum selenium concentration of about 70 µg/L. From these analyses, we found that the increases in mortality risk were of similar magnitude in individuals with SELENOP ≤3.23 mg/L and in those with selenium <70 µg/L (Tables 5 and 6).

The regression analyses show quite wide confidence intervals, probably due to the small sample sizes. Overall, however, our findings suggest that low levels of selenium or SELENOP increase the mortality risk in individuals with an eGFR ratio ≤ 0.9.

Table 5. Cox proportional hazards regression analysis evaluating the risk of all-cause mortality after 12 years in those (among the placebo group) with an eGFR ratio ≤0.9 (and without any selenium supplementation).

Variables	Beta Value	Hazard Ratio	T-Value	95% CI	*p* Value
Hypertension	−0.28	0.75	−0.75	0.36–1.59	0.46
Diabetes	−0.001	0.99	−0.002	0.43–1.59	0.99
Ischemic heart disease	0.62	1.85	1.60	0.87–3.95	0.11
SELENOP < 3.23 mg/L	1.21	3.36	2.60	1.35–8.35	0.009

Table 6. Cox proportional hazards regression analysis evaluating the risk of CV mortality after 12 years in those (among the placebo group) with an eGFR ratio ≤0.9 (and without any selenium supplementation).

Variables	Beta Value	Hazard Ratio	T-Value	95% CI	*p* Value
Hypertension	−0.26	0.77	−0.58	0.32–1.87	0.56
Diabetes	0.26	1.30	0.53	0.50–3.38	0.60
Ischemic heart disease	0.66	1.93	1.48	0.81–3.63	0.14
SELENOP < 3.23 mg/L	1.21	3.34	2.06	1.06–10.54	0.04

3.4. Effect of Selenium and CoQ10 Treatment on SPS Prevalence

In the group that was randomized to receive active treatment, 17 out of 145 (11.7%) had SPS (eGFR ≤ 0.7), while in the placebo group, 15 out of 138 (10.9%) had SPS (Chi2: 0.05, $p = 0.82$). After 48 months of active treatment, nine out of 110 (8.2%) had SPS. During the intervention period, nine participants with SPS at inclusion had increased their ratio above 0.7 at 48 months and exceeded the cut-off level for SPS, thereby returning to the healthy category. At the same time, two participants had decreased their ratio to ≤0.7 after 48 months, entering the SPS group. In the placebo group, 17 out of 96 (17.7%) had SPS (Chi2: 4.22, $p = 0.04$). Among the participants belonging to the placebo group, the corresponding number leaving the SPS group was four, while 13 participants newly fulfilled the definition for SPS (the individuals who were lost from the analysis had either died during the follow-up or had missing blood samples).

3.5. Effect of Selenium and CoQ10 Treatment on eGFR Ratio

We further evaluated the effect of the intervention using the eGFR ratio as a continuous variable and examined values of the active and placebo groups before and after intervention at 48 months among participants from both groups surviving the intervention period. Before the intervention, both groups had a similar mean (±SD) and median (10 and 90 perc.), eGFR ratio (active: mean 0.94 ± 0.22, median 0.90 (0.70; 1.22) and placebo: mean 0.93 ± 0.22, median 0.91 (0.70; 1.17), whereas after the intervention the eGFR ratio increased in the group receiving active treatment, while it remained similar in the placebo group. Hence, at 48 months the two groups differed significantly: active, mean 1.03 ± 0.18, median 0.98 (0.85; 1.25; $p = 0.33$); placebo, mean 0.89 ± 0.36, median 0.86 (0.52; 1.13; $p = 0.006$). A repeated measures analysis of variance was applied, which confirmed the difference ($p = 0.001$) between the groups (Figure 4). The effect size of the intervention was moderate ($d = 0.49$). *p*-values are specified as baseline between-group, follow-up between-group, within-group, or interaction statistics.

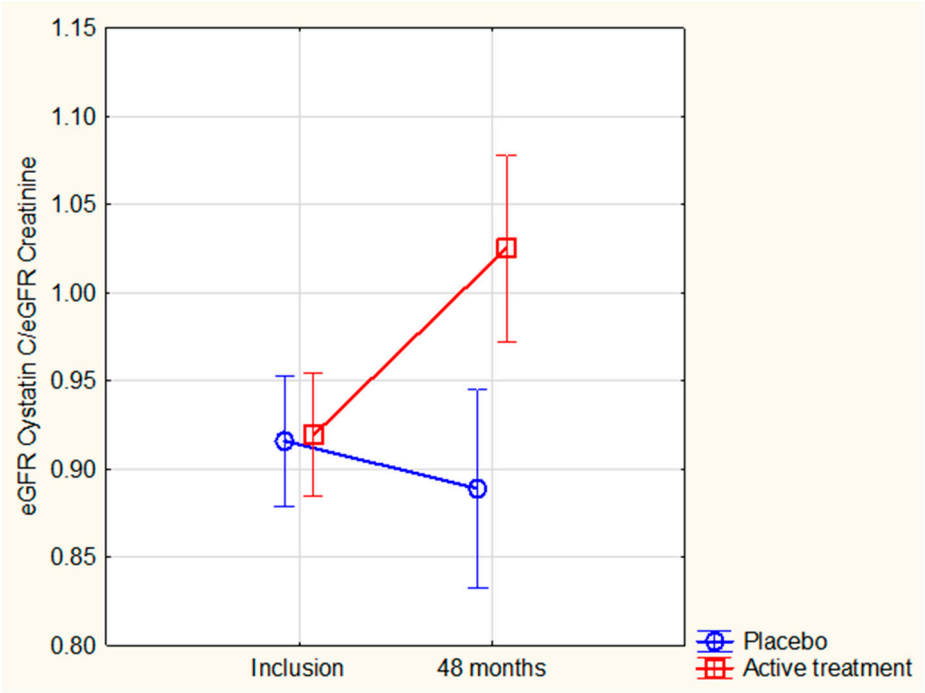


Figure 4. eGFRCystatin C/eGFRCreatinine ratio in the active treatment group compared with the placebo group in the total study population at inclusion and after 48 months. Evaluation performed using repeated measures of variance methodology. Note: Vertical bars denote 0.95 confidence intervals. Blue curve: Placebo; Red curve: Active treatment. Note: Current effect: $F(1, 204) = 11.87$, $p = 0.001$.

The distribution of the eGFR ratios at inclusion and after 48 months was evaluated using the eGFR ratios as continuous variables, comparing the active treatment and the placebo groups, as shown in Figure 5. Here, it can be seen that both the intervention in the actively treated group and the natural course in the placebo group over 48 months had a major impact on the lower end of the distribution. The supplementation caused a major reduction in participants having SPS at inclusion, while it also appeared to increase the eGFR ratio among non-SPS participants. In the placebo group, the eGFR ratio distribution curve flattened, and the lower end of the distribution increased, with a significant number of non-SPS participants at baseline entering the SPS group.

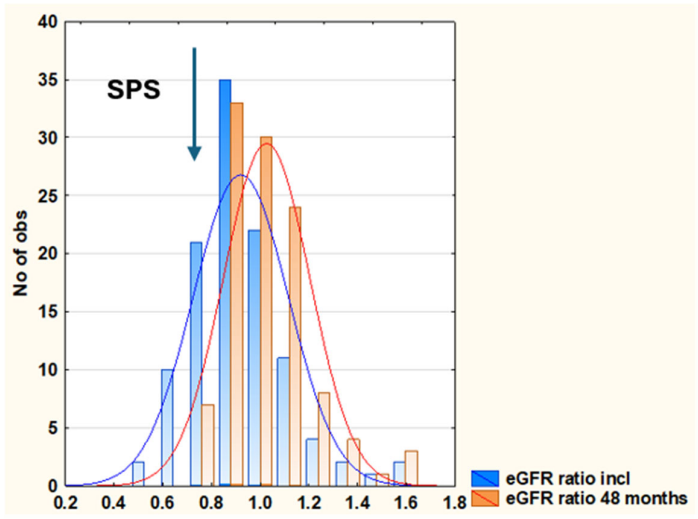


Figure 5. *Cont.*

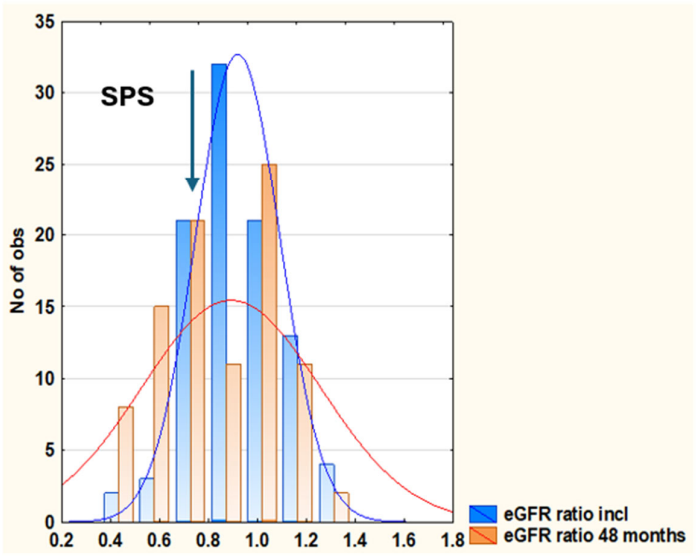


Figure 5. Histogram and normalized curves showing the distribution of eGFR ratios at inclusion (blue) and after 48 months (red). Panel (**red**): the active treatment group. Panel (**blue**): the placebo group. Arrow: cut-off: ≤0.7.

3.6. Association Between GPx3 and the eGFR Ratio

We previously found that GPx3 at inclusion was inversely correlated with creatinine and more so with cystatin C [43]. A positive correlation was found for the corresponding eGFRs. We also found that GPx3 at inclusion, for the active group, correlated weakly with the improvement in eGFR at 48 months. We therefore examined the relationship between GPx3 at inclusion and the eGFR ratio in a subgroup for which GPx3 had been determined. At inclusion, we found that GPx3 correlated with the eGFR ratio ($r = 0.37$, $p = 0.001$) (Figure 6).

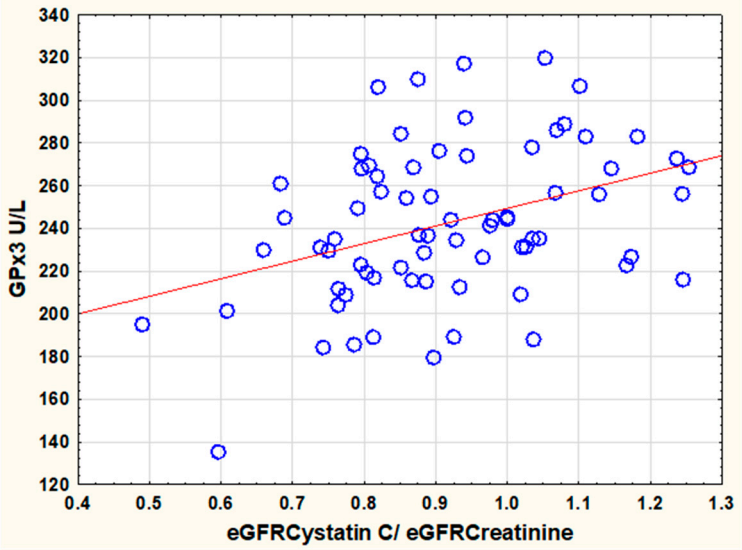


Figure 6. Scatterplot showing the relation between GPx3 and the eGFRCystatin C/eGFRCreatinine ratio in the study population at inclusion. Note: $r = 0.37$; $p = 0.0012$; $r^2 = 0.14$.

3.7. Impact of the Intervention on Mortality Among Participants with SPS

To assess the effect of supplementation on long-term mortality among participants with SPS, a Kaplan–Meier analysis of all-cause mortality was performed (Figure 7).

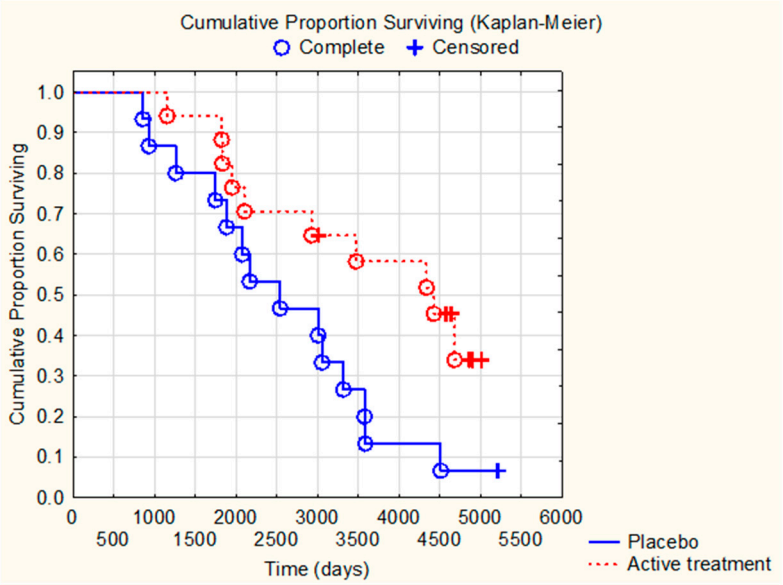


Figure 7. Kaplan–Meier graph illustrating all-cause survival in the SPS groups receiving the active treatment compared with the placebo group within a follow-up period of 12 years. Note: Z = −1.97; $p = 0.048$. Blue curve: Placebo; Red curve: Active treatment.

Despite the small number of participants in the two groups (17 in the active treatment group and 15 in the placebo group), the analysis showed significantly higher survival among participants receiving active treatment than among those receiving a placebo ($p = 0.048$). The findings in the SPS subgroup should be regarded as exploratory and hypothesis-generating because of the small sample size and wide confidence intervals.

By applying a Cox proportional hazards regression analysis, it became evident that, even when adjusted for several covariates influencing the risk of all-cause mortality and despite a wide confidence interval, a relatively strong and statistically significant risk reduction occurred with supplementation with selenium/CoQ10 according to the model (HR: 0.36; $p = 0.02$) (Table 7). The wide confidence intervals in all Cox regressions performed are mainly explained by the small sample sizes evaluated.

Table 7. Cox proportional hazards regression analysis evaluating the risk of all-cause mortality after supplementation with selenium and coenzyme Q10 combined in a multivariate model after 12 years of follow-up preceded by four years of intervention in an SPS population.

Variables	Beta Value	Hazard Ratio	T-Value	95% CI	*p* Value
Hypertension	−0.12	0.89	−0.26	0.36–2.18	0.80
Diabetes	0.83	2.30	1.26	0.63–8.42	0.21
Active treatment	−1.01	0.36	−2.29	0.16–0.86	0.02

To compare the all-cause mortality risks in a non-SPS population, we conducted a corresponding Cox proportional hazards regression analysis. We found that active supplementation had no significant effect on mortality risk in this population (HR: 0.90; $p = 0.59$) (Table 8).

The effect on CV mortality by supplementation was likewise evaluated, first through a Kaplan–Meier analysis. This showed a significant difference between the two groups, in favor of the active treatment group ($p = 0.034$) (Figure 8).

Table 8. Cox proportional hazards regression analysis evaluating the risk of all-cause mortality after supplementation with selenium and coenzyme Q10 combined in a multivariate model after 12 years of follow-up preceded by four years of intervention in a non-SPS population.

Variables	Beta Value	Hazard Ratio	T-Value	95% CI	*p* Value
Hypertension	0.32	1.37	1.40	0.88–2.14	0.16
Diabetes	0.37	1.44	1.68	0.94–2.21	0.21
Active treatment	−0.10	0.90	−0.54	0.63–1.30	0.59

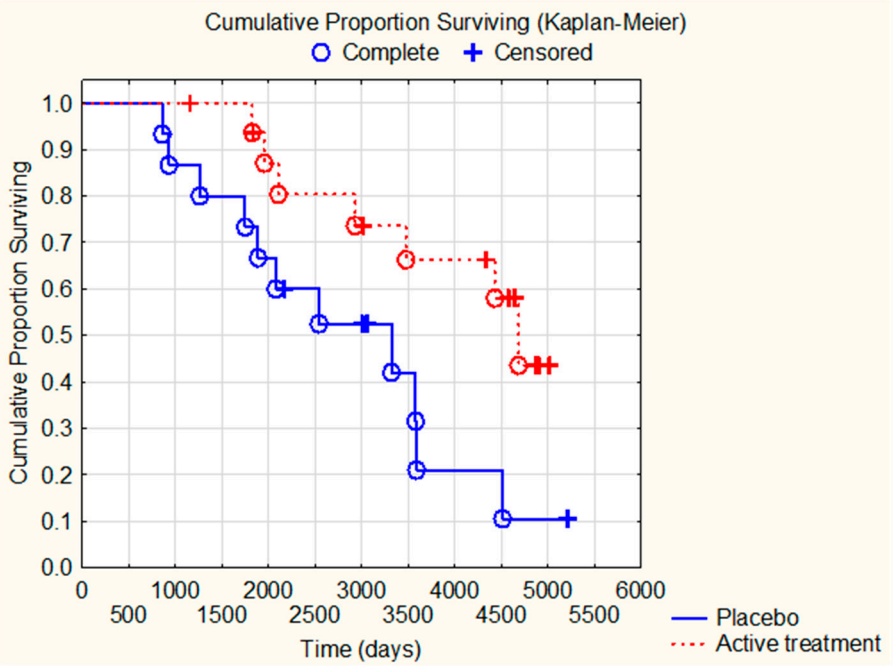


Figure 8. Kaplan–Meier graph illustrating survival from CV mortality in the SPS groups receiving active treatment group compared with the placebo group within a follow-up period of 12 years. Note: $Z = -2.12$; $p = 0.034$. Blue curve: Placebo; Red curve: Active treatment.

In order to evaluate the risk reduction, a Cox proportional hazards regression analysis was performed, which demonstrated a significant risk reduction with supplementation, even after adjusting for some specific cardiovascular risk-related covariates (HR: 0.31; $p = 0.02$) (Table 9).

Table 9. Cox proportional hazards regression analysis evaluating the risk of CV mortality after supplementation with selenium and coenzyme Q10 combined in a multivariate model after 12 years of follow-up preceded by four years of intervention in an SPS population.

Variables	Beta Value	Hazard Ratio	T-Value	95% CI	*p* Value
Hypertension	0.19	1.21	0.35	0.41–3.59	0.73
Ischemic heart disease	−0.28	0.75	−0.46	0.23–2.51	0.64
Active treatment	−1.18	0.31	−2.26	0.11–0.85	0.02

To compare the CV risks in a non-SPS population, we conducted a corresponding Cox proportional hazards regression, which showed that supplementation also reduced CV mortality risk among participants without SPS (non-SPS) (HR: 0.58; $p = 0.04$) (Table 10).

Table 10. Cox proportional hazards regression analysis evaluating the risk of CV mortality after supplementation with selenium and coenzyme Q10 combined in a multivariate model after 12 years of follow-up preceded by four years of intervention in a non-SPS population.

Variables	Beta Value	Hazard Ratio	T-Value	95% CI	*p* Value
Hypertension	0.29	1.34	0.97	0.74–2.42	0.33
Ischemic heart disease	0.96	2.61	3.66	1.56–4.37	<0.001
Active treatment	−0.54	0.58	−2.11	0.35–0.96	0.04

4. Discussion

In this elderly community-living population, the eGFR ratio emerged as a powerful predictor of long-term mortality risk. Individuals with an eGFR ratio ≤ 0.7 experienced higher all-cause and cardiovascular mortality over 12 years, confirming previous reports that SPS constitutes a state of systemic vulnerability. The strong association between a low eGFR ratio and adverse outcomes has been reported to persist even in participants with preserved renal filtration rate (absolute eGFR values), underscoring the clinical importance of including cystatin C and evaluating discordance between filtration markers rather than relying on creatinine alone when assessing renal function [8]. Retention of proteins with molecular mass below 30 kDa, which include cytokines and other mediators of inflammation and several proteins known to promote cardiovascular disease, has been suggested to link SPS with an increased risk of CV morbidity and mortality [9,50].

The biological mechanisms underlying SPS remain incompletely understood, and the mechanisms presented below should be regarded as hypothetical. Accumulating evidence, however, suggests that endothelial dysfunction and oxidative stress may impair the filtration of low-molecular-weight proteins such as cystatin C [47]. This aligns with the present findings, where supplementation with selenium and CoQ10—two agents known to enhance antioxidant capacity [51] and reduce inflammatory burden [24] and endothelial dysfunction [52], as previously shown by our group—significantly reduced the prevalence of SPS over 48 months. The improvement in the eGFR ratio in the supplemented group, as well as the deterioration in placebo-exposed subjects, might suggest that oxidative stress and inflammation contribute to the selective reduction in cystatin C filtration characteristic of SPS. Selenium has a central role in renal function [26], as illustrated by the association between plasma selenoprotein GPx3 [43], mainly synthesized by the kidneys, and eGFR ratio. We and others have shown that GPx3 is reduced in kidney failure. Here, we speculate that reduced synthesis of GPx3 at lower eGFR ratios (SPS) might be due to impaired filtration of SELENOP (≈55 kDa) and fragments (≈20 kDa) into primary urine. As the main source of selenium to the kidney operates by LPR2-(megalin) mediated uptake of SELENOP and fragments from primary urine by the proximal tubular cells, SPS might result in a reduced supply of selenium for synthesis of GPx3, which is also an important protector against vascular thrombosis [29,52–54]. Also, the selenium level as well as the SELENOP level at inclusion have a significant inverse association with the risk of future CV mortality, as could be seen in our 12-year analysis of the untreated group, which provides further support for one possible mechanistic link to selenium. Participants receiving selenium and CoQ10 experienced lower all-cause and cardiovascular mortality and decreased cardiovascular risk even after adjusting for central risk factors. The magnitude of risk reduction seemed even greater among individuals with SPS, a subgroup characterized by high baseline vulnerability. Although the sample size for the SPS participants was small (≈11%), we argue that the SPS participants did not differ significantly from the non-SPS participants in relevant covariates at baseline, and the consistency of the findings across analytical approaches strengthens the inference that supplementation in a group low in

selenium may mitigate the pathological processes driving SPS and its associated mortality risk. While the proposed SELENOP filtration and GPx3 synthesis pathway was not directly tested and remains speculative in human subjects, a similar mechanism has been suggested by transgenic mouse models [53].

These results also reinforce the value of incorporating cystatin C into routine renal assessment, particularly in elderly populations where creatinine-based estimates may be misleading due to reduced muscle mass. The eGFR ratio provides additional prognostic information beyond either marker alone, as the ratio also seems to deteriorate progressively in individuals with a ratio above 0.7, and may help identify, early in the disease course, individuals who would benefit from targeted interventions. Regarding the significance of selenium status, this study accords with a recent observational study in 570 patients with heart failure, where low SELENOP concentrations were associated with having an eGFR ratio qualifying for SPS and acute kidney injury and hospitalization [55]. Importantly, our data support the notion that a targeted intervention with selenium and CoQ10, particularly in those with low selenium status, seems to positively impact disease course, kidney function, and survival odds.

Limitations of the study should be acknowledged. The study population was small, resulting in wide confidence intervals in the analyses and limiting the possibility of including more covariates. This, in turn, limits the interpretation of the obtained results. The included population was geographically homogeneous, which may limit the generalizability. The mechanistic pathways linking supplementation to improvements in the eGFR ratio were not directly assessed, and residual confounding therefore cannot be excluded. Nonetheless, the randomized design, long follow-up period (12 years), assessment of selenium status by two complementary biomarkers reducing the risk of misclassification, and the consistent mortality findings support the robustness of the conclusions. Long-term storage of the blood samples may have introduced analytical variability and should therefore also be regarded as a potential limitation.

A further limitation is the potential for selection bias. The present exploratory sub-study included 283 of the 443 participants in the original randomized trial, as inclusion required available baseline measurements of both creatinine and cystatin C for calculation of the eGFR ratio. Consequently, the analyzed population may not be fully representative of the original randomized cohort. Although baseline characteristics were comparable between the active treatment and placebo groups within the present sub-study, this does not rule out systematic differences between participants included in the present analyses and those who were not. Selection related to availability of biological samples or complete renal biomarker data could therefore have influenced the observed prevalence of SPS and its associations with mortality. In addition, analyses based on measurements at 48 months were restricted to participants who survived and had blood samples available at follow-up, introducing a potential survivor/attrition bias. This is particularly relevant when interpreting changes in SPS prevalence and the eGFR ratio over time. Nevertheless, because treatment allocation was randomized in the original trial, selection for the present sub-study would not necessarily bias the treatment comparison unless the availability of samples or follow-up measurements differed in relation to both treatment allocation and outcome. These considerations further support interpreting the subgroup findings as exploratory and hypothesis-generating.

5. Conclusions

In summary, this study demonstrates that SPS is a clinically meaningful phenotype associated with substantially increased mortality, particularly in those with a low selenium status, and that long-term supplementation with selenium and CoQ10 seems to improve eGFR ratio in SPS, reduce the incidence of SPS and its progression, and thereby improve the survival rate. These findings highlight the potential for selenium and CoQ10 interventions to reduce renal and cardiovascular risk in elderly individuals with a low selenium status and support broader clinical adoption of the eGFR ratio as a prognostic tool. However, the results should be regarded as hypothesis-generating, and further research is required to confirm them.

Author Contributions: Conceptualization, A.L., U.A., A.G., J.A. (Jan Alexander), L.S. and J.A. (Jan Aaseth); Methodology, A.L., U.A. and A.G.; Validation, U.A., A.L., J.A. (Jan Alexander) and J.A. (Jan Aaseth); Formal Analysis, A.L., U.A. and A.G.; Investigation, U.A. and A.L.; Resources, U.A. and A.L.; Data Curation, U.A.; Writing—Original Draft Preparation, A.L., U.A., A.G., J.A. (Jan Aaseth), J.A. (Jan Alexander) and L.S.; Supervision, A.L.; Funding Acquisition, U.A. and A.L. All authors have read and approved the final manuscript.

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Institutional Review Board Statement: The study was approved by the Regional Ethics Committee (Forskningsetikkommit-tén, Hälsouniversitetet, SE-581 85 Linköping, Sweden; approval no. D03-176, approval date, 6 May 2003) and was conducted in accordance with the ethical principles of the Declaration of Helsinki (1975). Review by the Medical Products Agency was not required, as the study did not involve the investigation of a medicinal product for a specific disease but focused on commercially available food supplements. The trial was registered at ClinicalTrials.gov (identifier: NCT01443780; registration date, 28 September 2011); registration was completed retrospectively, as prospective registration was not mandatory at the time of study initiation.

Informed Consent Statement: Written informed consent was obtained from all participants prior to enrolment.

Data Availability Statement: Under Swedish Law, the authors cannot share the data used in this study and cannot conduct any further research other than what is specified in the ethical permissions application. The dataset contains health-related personal data collected from human research participants and is therefore subject to Swedish and European data-protection legislation. Access to the data is restricted by The EU General Data Protection Regulation (GDPR; Regulation (EU) 2016/679), together with the Swedish Data Protection Act (SFS 2018:218), which govern the processing and disclosure of personal data. Processing of research data containing personal data requires an appropriate legal basis and safeguards. It is also restricted by The Swedish Ethical Review Act (Lag (2003:460) which requires ethical approval for research involving sensitive personal data and human participants. Secondary use of the data for new research purposes may require additional ethical review and approval. The Swedish Public Access to Information and Secrecy Act (Offentlighets- och sekretesslag 2009:400), which may restrict disclosure of research data containing identifiable personal information. For inquiries about the data, researchers should first contact the owner of the database, the University of Linköping. Please contact the corresponding author with requests for and assistance with data. If the university approves the request, researchers can submit an application to the Regional Ethical Review Board for approval to investigate their specific research question.

Conflicts of Interest: L.S. holds shares of selenOmed GmbH, a company involved in Se status assessment. All other authors declare no conflicts of interest.

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