placebo-controlled trial of coenzyme Q10 in Huntington disease

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ABSTRACT

Objective: To test the hypothesis that chronic treatment of early-stage Huntington disease (HD) with high-dose coenzyme Q10 (CoQ) will slow the progressive functional decline of HD.

Methods: We performed a multicenter randomized, double-blind, placebo-controlled trial. Patients with early-stage HD (n = 609) were enrolled at 48 sites in the United States, Canada, and Australia from 2008 to 2012. Patients were randomized to receive either CoQ 2,400 mg/d or matching placebo, then followed for 60 months. The primary outcome variable was the change from baseline to month 60 in Total Functional Capacity score (for patients who survived) combined with time to death (for patients who died) analyzed using a joint-rank analysis approach.

Results: An interim analysis for futility revealed a conditional power of <5% for the primary analysis, prompting premature conclusion in July 2014. No statistically significant differences were seen between treatment groups for the primary or secondary outcome measures. CoQ was generally safe and well-tolerated throughout the study.

Conclusions: These data do not justify use of CoQ as a treatment to slow functional decline in HD.

ClinicalTrials.gov identifier: NCT00608881.

Classification of evidence: This article provides Class I evidence that CoQ does not slow the progressive functional decline of patients with HD. *Neurology*® 2017;88:152–159

GLOSSARY

CI = confidence interval; **CoQ** = coenzyme Q10; **DSM-IV-R** = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, revised*; **HD** = Huntington disease; **HR** = hazard ratio; **TFC** = Total Functional Capacity; **UHDRS** = Unified Huntington's Disease Rating Scale.

Huntington disease (HD) is a progressive neurodegenerative disease.[1,2] While symptomatic treatments are available, there is no therapy to delay onset or slow progression.[3–5] Substantial experimental evidence suggests defective energetics in HD pathology.[6–16] As such, agents that improve mitochondrial function and reduce oxidative stress are rational candidates for study. This notion is reinforced by observations that several agents that improve mitochondrial

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function ameliorate pathologic features in HD mouse models.[17–20] One such agent, coenzyme Q10 (CoQ), has demonstrated beneficial properties in experimental models of amyotrophic lateral sclerosis,[21] Parkinson disease,[22] and some models of HD.[18,23] CoQ plays a central role in oxidative phosphorylation, appears to stabilize membranes, acts as an antioxidant,[24] and may influence vesicle migration, cell growth, and signal transmission.[25]

In the CARE-HD clinical trial, 347 patients with early HD were randomized to receive CoQ 300 mg twice daily, remacemide hydrochloride 200 mg twice daily, both, or neither for 30 months.[26] Those receiving CoQ did not demonstrate a substantial benefit in outcome measures compared to placebo, but a nonsubstantial trend towards slowed decline compared to controls over 30 months was observed, as determined by Total Functional Capacity (TFC) score (mean decline of 2.40 vs 2.74 points, $p = 0.15$) as well as the Functional Checklist and Independence Scale scores.[27] It was unclear if these observations represented actual clinical efficacy. After establishing a maximal tolerable dose based on preclinical studies,[28] we sought to address these issues by evaluating the effect of a higher dosage of CoQ in a large group over a 5-year follow-up period.

METHODS Details concerning several aspects of the Methods, including randomization and blinding, additional eligibility criteria, CoQ assay and CAG analysis/genotyping, study visits, dosage modifications, secondary outcome variables, assumptions underlying the sample size determination, methods for statistical analysis, and interim analyses can be found in appendix e-1 at Neurology.org.

Study design and organization. This multicenter randomized, double-blind, placebo-controlled clinical trial was conceived and conducted by the Huntington Study Group and sponsored by the National Institute of Neurological Disorders and Stroke. The trial was designed to test the hypothesis that chronic treatment of patients with early-stage HD with high-dosage CoQ (2,400 mg/d) will slow the functional decline of HD over a follow-up period of 60 months (Level I evidence).

The study is listed on ClinicalTrials.gov (NCT00608881).

Standard protocol approvals, registrations, and patient consents. This study was approved by the institutional review boards at 48 participating sites in the United States, Canada, and Australia. All participants provided written informed consent. The National Institute of Neurological Disorders and Stroke–appointed independent Data and Safety Monitoring Board monitored the progress of the trial.

Randomization and enrollment. A total of 609 participants with early-stage HD were enrolled at 48 sites. Patients were randomly assigned with equal allocation to CoQ 2,400 mg/d or matching placebo, administered in twice daily dosage.

Eligibility criteria. Patients were required to meet the following core criteria within 28 days prior to randomization: (1) clinical features of HD, with a confirmatory family history of HD or a CAG repeat expansion ≥36; (2) TFC ≥9 at the baseline visit; (3) ambulatory and not requiring skilled nursing care; (4) age ≥16 years; (5) unable to become pregnant or using adequate birth control methods beginning 60 days prior to the baseline visit; (6) stable dosages of psychotropic medications. Patients were excluded due to (1) known sensitivity or intolerability to CoQ; (2) exposure to any investigational agent within 30 days of baseline; (3) unstable medical illness; (4) unstable psychiatric illness within 90 days of baseline; (5) substance abuse (DSM-IV-R criteria) within 1 year of baseline; (6) pregnancy or breast-feeding; (7) use of supplemental CoQ within 30 days prior to baseline; (8) clinically relevant abnormalities in screening laboratories; (9) allergy.

Study visits. Study visits consisted of a screening visit, baseline visit, and follow-up visits at months 1, 3, and 6, and every 6 months thereafter through month 60. Telephone calls were conducted at month 9 and every 6 months thereafter through month 57 to monitor concomitant medication use, compliance with study medication, and adverse events. At the screening visit, after the patient provided written informed consent, eligibility criteria were checked, a medical history was taken, vital signs (blood pressure, pulse, weight) were measured, and blood was drawn for safety laboratory tests (serum chemistry, hematology, pregnancy test, urinalysis) and for the CoQ level assay. A baseline visit was scheduled to occur within 28 days of screening, at which time confirmation of a research proxy with whom the site investigator could discuss the patient's wishes about future study participation in the event of loss of cognitive capacity was required. A final eligibility check was performed and a blood sample was obtained for CAG analysis/genotyping.

At baseline and all follow-up visits, patients were assessed for capacity to consent (beginning at month 6), concomitant medication use, TFC (except month 1), modified Rankin Scale[29] score (beginning at month 3), vital signs, and adverse events. The patient's dosage log and counts of pills dispensed and returned were also reviewed to monitor compliance. The Unified Huntington's Disease Rating Scale (UHDRS)[27] was administered at baseline and annually thereafter. Safety laboratory tests and an assay for plasma CoQ level were collected at baseline, month 3, and annual visits. Physical and neurologic examinations were performed at baseline and at months 36 and 60. Throughout the study, patients were allowed to stop study drug at any time (consent withdrawal, intolerance) and continue participation in scheduled assessments off study drug.

Study intervention. CoQ (2,3-dimethoxy-methylbenzoquinone, or ubiquinone) and matching placebo were obtained from Enzymatic Therapy, Inc. (Green Bay, WI). Patients started taking CoQ as a 300 mg chewable wafer or matching placebo orally twice daily, followed by a subsequent 4-week titration towards a maintenance dosage of 2,400 mg/d. This dosage was selected based on considerations of tolerability and achieved plasma CoQ levels in a preliminary study.[30]

Outcome variables. The primary outcome variable was a rank based on a combination of time to death (for patients who died) and change in TFC score from baseline to month 60 (for patients who survived), as explained in the supplementary material.

Table 1	Baseline characteristics of trial participants	
Variable	CoQ (n = 303)	Placebo (n = 306)
Age, y	50.5 (11.9)	50.7 (11.6)
Male	50.8	46.4
White	93.7	95.1
Education ≤12 years	32.3	30.1
Medical history		
Depression	62.1	55.6
Obsessive-compulsive disorder	7.6	10.8
Psychosis	1.3	3.3
Suicidal ideation	13.2	13.1
Suicide attempts	5.9	4.6
Affected parent		
Mother	45.5	47.7
Father	40.3	42.5
Unknown/missing	14.2	9.8
Years since HD onset	4.6 (4.2)	4.9 (4.6)
Years since HD diagnosis	3.1 (3.4)	3.0 (3.3)
CAG repeat length	44.1 (4.1)	43.9 (3.8)
Total Motor score	28.1 (13.3)	27.5 (13.9)
Behavioral Frequency score	6.2 (5.9)	5.9 (5.7)
Behavioral Frequency × Severity score	12.0 (14.1)	11.1 (13.2)
Symbol Digit Modalities Test	28.9 (11.5)	29.9 (12.1)
Verbal Fluency Test	25.4 (11.6)	26.7 (12.2)
Stroop Interference Test		
Color naming	52.1 (17.3)	51.6 (16.4)
Word reading	64.2 (20.2)	65.1 (18.5)
Interference	30.5 (10.9)	29.6 (11.2)
Functional Checklist score	22.7 (2.3)	22.9 (2.2)
Independence Scale score	89.1 (9.1)	90.0 (8.8)
Total Functional Capacity score	10.8 (1.5)	11.0 (1.5)

Abbreviations: CoQ = coenzyme Q10; HD = Huntington disease.
Values are mean (SD) or %.

Secondary outcome variables were derived from the UHDRS and are described in detail in the supplementary material.

Sample size determination. A sample size of 609 patients was planned to provide 90% power to detect a group difference of 1.0 point in the mean 60-month change in TFC score, using a *t* test and a 5% significance level (2-tailed), after accounting for 15% withdrawal over time.

Statistical analysis. The primary analysis was performed using a joint rank approach[31] whereby patients are ranked from worst to best outcome with patients who die being assigned the worst ranks (and ranked according to the time of death) and patients who survive being ranked more favorably in order of the change from baseline to month 60 in TFC score. This analysis yields an estimated probability that a randomly selected patient treated with CoQ has a better outcome than a randomly selected patient treated with placebo, along with its associated 95% confidence interval (CI) and *p* value.

Analyses of secondary outcome variables were performed using the joint rank approach, repeated-measures analysis of covariance models, and Cox proportional hazards models depending on the nature of the outcome variable.

All analyses were performed in accordance with the intention-to-treat principle and included all available data from all randomized patients.

RESULTS Baseline characteristics. A total of 668 patients were screened, with 609 randomized between March 19, 2008, and June 25, 2012. Demographic and clinical characteristics at baseline were comparable in the treatment groups (table 1).
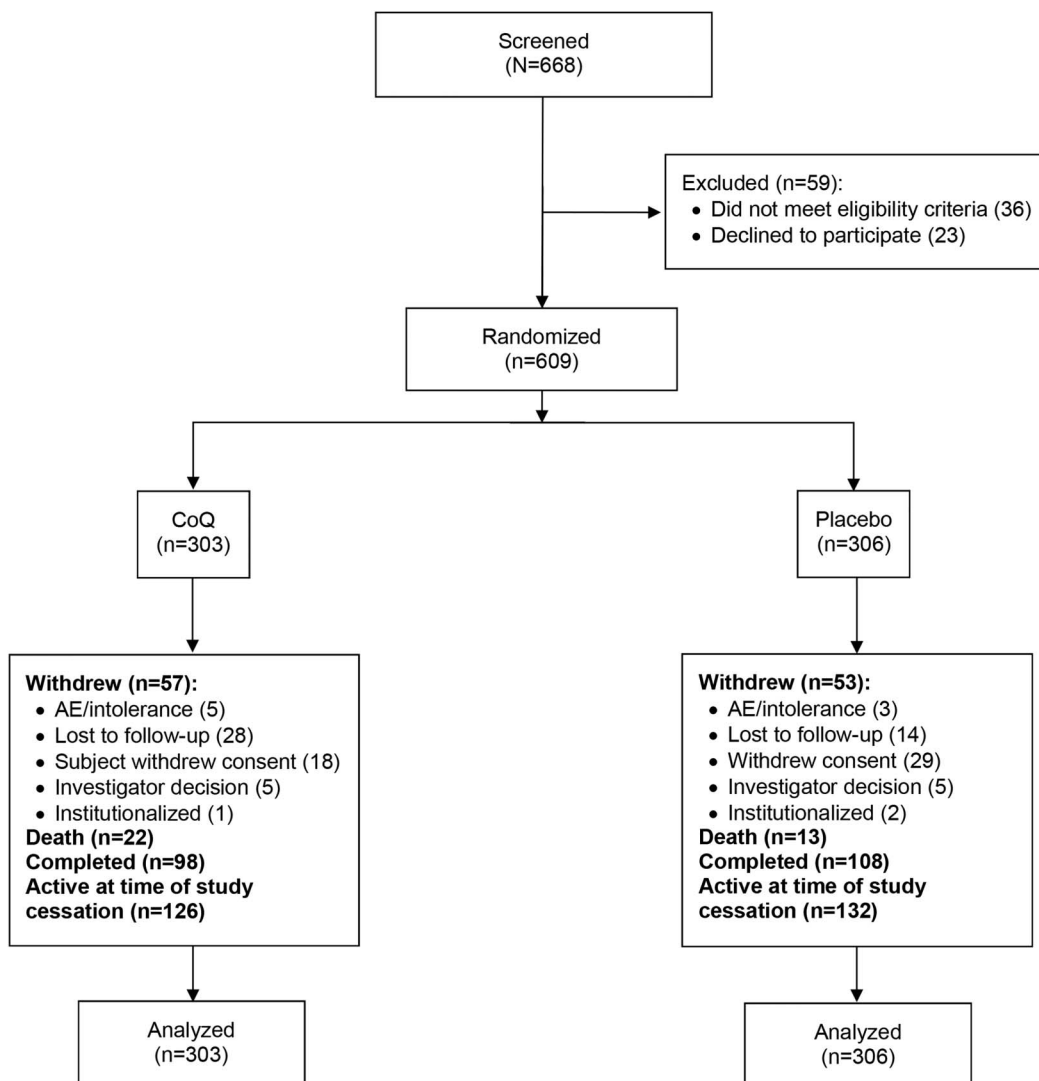
Patient disposition. At the time of study termination, of the 609 enrolled patients, 206 (34%) had completed the month 60 visit (25% on study drug and 9% off study drug), 258 (42%) were still active in the trial (34% on study drug and 8% off study drug), 110 (18%) had withdrawn participation in the trial while alive (12% on study drug and 6% off study drug at time of withdrawal), and 35 (5.7%) died during study participation (3.0% on study drug and 2.8% off study drug). The treatment groups were comparable with respect to patient disposition. There were more deaths observed in the CoQ group (n = 22, 7.3%) than in the placebo group (n = 13, 4.2%); this is discussed further below. In addition, 9 patients (5 in the CoQ group and 4 in the placebo group) died after having withdrawn participation in the study. At the time of study termination, 91% of patients had completed 1 year of follow-up, 83% had completed 2 years, 69% had completed 3 years, 52% had completed 4 years, and 34% had completed 5 years (figure 1).

Compliance with study drug. Compliance during the study was high in the 2 treatment groups (87.1% ± 15.8% for CoQ, 87.0% ± 16.7% for placebo). Median CoQ levels across visits ranged from 4.4 to 8.0 μg/mL in the CoQ group and from 0.8 to 1.0 μg/mL in the placebo group (figure e-1).

Tolerability and safety. CoQ was generally safe and well-tolerated. Forty-six dosage reductions occurred in 29 patients (11 placebo, 18 CoQ), most commonly for gastrointestinal disturbances in both groups. Thirteen of these patients (5 placebo, 8 CoQ) were discontinued from their assigned treatment for intolerance either by patient or investigator decision, while the remainder were able to continue on either a reduced or original dosage.

The most common adverse event categories, in order from highest to lowest percentage of patients experiencing at least one event, were psychiatric disturbances, infections, gastrointestinal disturbances, injury, and nervous system disturbances (table 2). There were no significant differences between groups in the frequency of individual adverse events with the

Figure 1 Patient disposition

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                        Screened
                        (N=668)
                           |
                           |------------------> Excluded (n=59):
                           |                    • Did not meet eligibility criteria (36)
                           |                    • Declined to participate (23)
                           |
                      Randomized
                      (n=609)
                           |
              +------------+------------+
              |                         |
           CoQ                       Placebo
          (n=303)                    (n=306)
              |                         |
   Withdrew (n=57):          Withdrew (n=53):
   • AE/intolerance (5)      • AE/intolerance (3)
   • Lost to follow-up (28)  • Lost to follow-up (14)
   • Subject withdrew        • Withdrew consent (29)
     consent (18)            • Investigator decision (5)
   • Investigator            • Institutionalized (2)
     decision (5)            Death (n=13)
   • Institutionalized (1)   Completed (n=108)
   Death (n=22)              Active at time of study
   Completed (n=98)          cessation (n=132)
   Active at time of study
   cessation (n=126)
              |                         |
         Analyzed                  Analyzed
         (n=303)                   (n=306)
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AE = adverse event; CoQ = coenzyme Q10.

exception of insomnia, which was less frequent in the CoQ group (11.6% vs 20.9%, $p = 0.002$). No substantial differences in safety laboratory findings were observed between groups.

A total of 238 serious adverse events were reported in 159 patients (27.1% of patients in the placebo group and 25.1% in the CoQ group). The majority were believed to be HD-related, and no substantial group differences were identified. Study personnel unaware of treatment group assignment categorized the 35 study deaths as either unrelated or related to HD, with related consisting of inanition, infection, accident/trauma, and suicide. Seventeen of the 22 deaths in the CoQ group (77.3%) and 9 of 13 in the placebo group (69.2%) were deemed HD-related. The most common non-HD related cause of death was malignancy (4 patients). There were 22 suicide attempts in the study, with 5 completed. Differences between groups regarding suicide attempts

(10 placebo, 12 CoQ) or completions (1 placebo, 4 CoQ) were not statistically significant. No deaths were believed to be related to study drug.

Primary outcome variable. The results of the joint rank analyses for the UHDRS functional outcomes, including TFC score, are shown in table 3. Since a majority of patients (60%) did not die or complete 60 months of follow-up, a large number of patients were ranked on the basis of outcomes at visits that occurred prior to month 60. For this reason, the analyses were repeated including only patients who had long follow-up durations ($\geq$42 months and 60 months). In the latter analyses, patients who died or withdrew from the trial were included if they were enrolled early enough to have been followed for the specified duration. The results indicate no substantial group differences with respect to these outcomes. The results did not change substantially when restricted to

Table 2   Adverse events by treatment group

Adverse event	CoQ (n = 303)	Placebo (n = 306)	p Value
Behavioral/Psychiatric	54.5 (418)	54.3 (419)	0.96
Depression	20.8 (85)	22.9 (86)	0.53
Insomnia	11.6 (42)	20.9 (73)	0.002
Anxiety	12.2 (42)	14.1 (51)	0.50
Irritability	11.9 (42)	12.4 (46)	0.84
Gastrointestinal	44.6 (292)	43.5 (297)	0.79
Diarrhea	12.2 (49)	14.0 (67)	0.50
Nausea	10.2 (37)	7.8 (28)	0.30
Constipation	8.6 (34)	7.2 (26)	0.52
Vomiting	8.6 (31)	7.5 (31)	0.63
Infectious	44.9 (288)	50.3 (372)	0.18
Urinary tract	10.9 (43)	15.0 (69)	0.13
Pharyngitis	8.9 (35)	11.1 (53)	0.37
Trauma/injury	38.3 (281)	44.8 (399)	0.10
Falls	24.4 (136)	28.1 (189)	0.30
Neurologic	38.3 (244)	43.1 (299)	0.22
Chorea	12.2 (48)	14.7 (61)	0.37
Imbalance	6.3 (20)	6.9 (23)	0.77

Abbreviation: CoQ = coenzyme Q10.
Values are the percentages of patients with at least one occurrence of the event during follow-up (total numbers of events, including multiple events per person, are given in parentheses).

deaths that were judged (prior to unblinding) to be HD-related (data not shown).

Secondary outcome variables. Treatment effects on the secondary outcome variables from the UHDRS are

Table 3   Results of joint rank analyses

Variable	π	95% CI	p Value
Total Functional Capacity score			
All patients	0.494	0.454-0.534	0.76
Patients completing ≥ month 42	0.494	0.449-0.539	0.80
Patients completing month 60	0.493	0.435-0.551	0.82
Functional Checklist score			
All patients	0.496	0.458-0.534	0.84
Patients completing ≥ month 42	0.495	0.453-0.547	0.82
Patients completing month 60	0.490	0.435-0.544	0.71
Independence Scale score			
All patients	0.490	0.452-0.527	0.59
Patients completing ≥ month 42	0.502	0.460-0.543	0.94
Patients completing month 60	0.499	0.445-0.554	0.98

Abbreviations: CI = confidence interval; CoQ = coenzyme Q10.
π is the estimate of the probability π that a randomly selected patient treated with CoQ has a better outcome than a randomly selected patient treated with placebo. Under the null hypothesis of no effect of CoQ, π = 0.50.

summarized in table 4. No substantial effects of CoQ were evident. The CoQ group had a smaller mean decline in Word reading score at month 60 than the placebo group (treatment effect = 3.88; 95% CI 0.31–7.44; $p = 0.03$), but this was an isolated finding that may be due to multiple testing. No treatment effects were apparent on the time-to-event outcomes, including time to a 2-point decline in TFC score or death (hazard ratio [HR] 0.99; 95% CI 0.81–1.20; $p = 0.88$), time to a 3-point decline in TFC score or death (HR 0.93; 95% CI 0.75–1.15; $p = 0.50$), time to a TFC score of 6 or less or death (HR 0.98; 95% CI 0.75–1.28; $p = 0.89$), time to institutionalization or death (HR 1.65; 95% CI 0.97–2.79; $p = 0.07$), and time to death (HR 1.89, 95% CI 0.92–3.89; $p = 0.09$). Kaplan-Meier estimates for cumulative event probabilities for these events by treatment group at 1, 2, 3, 4, and 5 years are reported in table e-1.

DISCUSSION In this study, no beneficial effect of CoQ was detected on the primary outcome variable, and the trial was concluded early on the basis of an interim analysis for futility. None of the secondary outcome variables demonstrated a beneficial effect of CoQ with the exception of the Word reading score on the Stroop test, which as a lone finding may be spurious. As such, the trial provides no evidence that CoQ slows the progression of functional decline in HD, and these data do not justify a recommendation for CoQ as a treatment in HD.

CoQ at 2,400 mg daily demonstrated good tolerability, with no serious or unexpected side effects emerging. Insomnia was less frequently reported in the CoQ arm, the reason for which is unclear. CoQ would be expected to exert an effect on a broad population of neuronal networks, given speculation for a general benefit on bioenergetics; it is not clear why insomnia, reported subjectively, would improve without broader suggestion of clinical benefit. Insomnia was not less common in CARE-HD patients treated with CoQ.[26] There were more deaths in the CoQ group, though the group difference in the frequency of death was not statistically significant. It seems unlikely that CoQ would cause greater mortality in HD. The frequency of HD-related (vs unrelated to HD) deaths was similar in the 2 groups, as was the frequency of suicide attempts. Evidence from our trial suggests that CoQ is not associated with undue risk of harm in the HD population, even though the observed number of deaths was higher in the CoQ group.

Possible explanations for the finding of no benefit of CoQ, other than the actual absence of an effect, include (1) the study lacked adequate power to detect an effect, (2) selected outcome measures were not

Table 4 Treatment effects on secondary outcome variables at month 60

Variable	Adjusted mean change		Treatment effect	95% CI	p Value
	CoQ (n = 303)	Placebo (n = 306)			
TFC score[a]	−4.53	−4.76	0.23	−0.44 to 0.91	0.50
Functional Checklist score[a]	−7.93	−8.02	0.09	−1.40 to 1.58	0.91
Independence Scale score[a]	−26.30	−24.86	−1.44	−6.68 to 3.79	0.59
Total Motor score	18.06	19.18	−1.12	−4.40 to 2.16	0.50
Behavioral Frequency score	1.39	1.43	−0.04	−1.48 to 1.39	0.95
Behavioral Frequency × Severity score	4.29	5.06	−0.77	−4.78 to 3.23	0.71
Symbol Digit Modalities Test	−10.95	−11.36	0.41	−1.32 to 2.14	0.64
Verbal Fluency Test	−5.07	−4.47	−0.60	−2.71 to 1.51	0.58
Stroop Interference Test					
Color naming	−14.21	−14.51	0.29	−2.28 to 2.87	0.82
Word reading	−15.25	−19.13	3.88	0.31 to 7.44	0.03
Interference	−7.57	−8.61	1.04	−1.10 to 3.18	0.34

Abbreviations: CI = confidence interval; CoQ = coenzyme Q10; TFC = Total Functional Capacity.
[a] For patients who died, a value of zero was imputed for visits scheduled to occur after the patient's death.
Treatment effect is the difference (CoQ − placebo) between the adjusted group mean changes from baseline to month 60 calculated from a repeated-measures analysis of covariance model; see text for details.

sensitive enough to detect an effect, or (3) the treatment duration was insufficient. These explanations are improbable. A plausible alternative explanation would be that CoQ cannot counteract the neurodegenerative process in manifest HD, at which time cellular rescue may be difficult or not influenced by CoQ. It is notable that reported benefit of CoQ in preclinical HD models is variable.[18,23] Considering the complexity and heterogeneity of neurodegeneration, as well as limitations inherent in preclinical models for representing human disease, interpreting data and generating hypotheses from preclinical neurodegenerative models remains challenging.

It is conceivable that a more efficient or concentrated delivery of CoQ to the brain may be more beneficial than the formulation studied here, or that efficacy can only be discernable if CoQ is given prior to the onset of symptoms, i.e., in at-risk patients. In that regard, investigators have studied creatine, a phosphate buffer that bolsters adenosine 5′-triphosphate levels, in asymptomatic carriers or at-risk patients with HD over 18 months.[32] No substantial differences in cognitive outcome measures were seen between groups, but radiographic measures demonstrated a substantial treatment effect on cortical and striatal atrophy. A similar approach—testing CoQ in patients with premanifest disease—may be reasonable. The current study did not use radiographic outcome measures, and the question of whether substantial treatment effects on imaging outcomes are of clinical importance over time has yet to be answered in HD. More quantitative outcome measures (e.g., Q-motor, accelerometry) may increase sensitivity to detect treatment effects, particularly subtle motor effects, though the clinical value of such observations may be ambiguous. Future studies of CoQ in presymptomatic patients, including imaging outcomes or quantitative assessments, may be worth considering given the tolerability of high-dosage CoQ.

Despite not demonstrating a beneficial effect of CoQ, the 2CARE trial has been a substantial study for HD therapeutics in terms of its methodology, duration of observation, long-term commitment of HD research participants, and the large amount of prospectively collected data. Further analyses of these data are expected to yield novel and useful information about the progression of HD that will be integral for planning future clinical studies. Our experience demonstrates the feasibility of the large simple study design in this population, in a setting where the evaluation of treatments aimed at slowing functional decline of chronic diseases will need to capture treatment effects over prolonged periods. It is also of value to consider how outcomes in the study of neurodegenerative diseases are selected. In diseases of this type, longer duration of follow-up can be expected to involve increased mortality; optimal handling of this issue remains a persistent challenge for clinical trialists in diseases such as amyotrophic lateral sclerosis.[33,34] Innovative approaches in the design and implementation of clinical trials for neurodegenerative conditions will continue to advance from studies like 2CARE.

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