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Original Research Article

Longitudinal Associations between Survival in Alzheimer's Disease and Cholinesterase Inhibitor Use, Progression, and Community-Based Services

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Key Words
Cognition · Activities of daily living · Home help services · Adult day care · Mortality · Statistical models

Abstract
Background/Aims: Factors including rate of disease progression, different aspects of cholinesterase inhibitor (ChEI) treatment, and use of community-based services might affect the longitudinal outcome of Alzheimer's disease (AD). Whether these factors alter life expectancy in AD is unclear. We therefore examined the association between long-term ChEI therapy and survival. ***Methods:*** The present study included 1,021 patients with a clinical diagnosis of AD and a Mini-Mental State Examination score of 10–26 at baseline from a 3-year, prospective, multicenter study of ChEI therapy in clinical practice. The relationship of potential predictors with mortality was analyzed using Cox regression models. ***Results:*** After up to 16 years of follow-up, 841 (82%) of the participants had died. In the Alzheimer's Disease Assessment Scale-cognitive subscale, a mean decline of ≥4 points/year or ≥2 points/year on the Physical Self-Maintenance Scale was a risk factor for an earlier death. In the multivariate models, longer survival was associated with higher ChEI dose and longer duration of treatment. Users of community-based services at baseline exhibited a 1-year shorter mean life expectancy than nonusers. ***Conclusion:*** A longer survival time can be anticipated for AD patients with slower deterioration who receive and tolerate higher ChEI doses and a longer duration of treatment.

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Introduction

Alzheimer's disease (AD) is a progressive degenerative disorder that eventually affects all aspects of a patient's life. A gradual deterioration of memory, orientation, decision making, and communication is accompanied by impaired performance of activities of daily living (ADL) tasks [1]. The loss of independence leads to years of disability in remaining life with increasing need of community-based care [2]. However, AD implies a shorter life expectancy compared with the general population. Our group showed that the mean survival time after a diagnosis of AD was 5 years for men and 6 years for women [3], whereas Statistics Sweden reports an average life expectancy of 11 years for a corresponding 75-year-old man and 13 years for a woman [4]. However, a direct association between AD and mortality is difficult to determine because most individuals affected by AD are older and have other somatic illnesses.

There are no curative therapies for AD. Cholinesterase inhibitors (ChEIs) are the predominant recommended treatment for mild-to-moderate AD, and they function by increasing the level of acetylcholine in neuronal synaptic clefts in the brain. These drugs may improve or stabilize some of the symptoms of AD for a limited period of 6–12 months on average [5]. Moreover, long-term observational studies of AD have described the benefits of ChEI on cognition [6, 7] and function [8, 9] over several years. We observed slower disease progression in patients with a higher cognitive or ADL ability at the start of therapy [9, 10], which suggests advantages of early initiation of ChEIs. Higher doses have previously been associated with better longitudinal cognitive and functional outcomes [9–11]. In addition, significant relationships between a higher dose of ChEI and less use of home help services [12] and delayed need for institutionalization [13] have been reported.

Whether different aspects of long-term treatment with ChEI, such as type of drug agent, dose, or duration, alter the lifespan in AD is unclear because few studies have investigated these associations. Conflicting outcomes regarding ChEI usage and its effect on survival have been reported [14, 15]. Duration of treatment was not reported to affect mortality for tacrine [16] or second-generation ChEIs [17]. A recent study from our group found that AD patients who improved or stabilized after 6 months of ChEI therapy live, on average, 6 months longer than those who worsened [18].

The aims of this longitudinal study of AD were (1) to investigate the relationships between measures of disease progression, ChEI treatment, and mortality, and (2) to examine the effect of community-based service use on survival time.

Materials and Methods

Participants and Setting

The Swedish Alzheimer Treatment Study (SATS) was started in 1997 to investigate the long-term effectiveness of ChEI treatment (donepezil, rivastigmine, galantamine) in a routine clinical setting and to evaluate the longitudinal course of AD from different perspectives. The SATS is a 3-year, observational, open-label, nonrandomized, multicenter study that has been previously described in several publications [3, 6, 9, 10, 12, 18, 19]. Briefly, outpatients who received a clinical diagnosis of dementia as defined by the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)* [20] and of possible or probable AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [21] were considered for inclusion. Moreover, the participants had to be community dwelling at the time of diagnosis, to have an identified caregiver, and to be assessable with the Mini-Mental State Examination (MMSE) [22] at the start of ChEI therapy (baseline). In total, 1,258 participants were prospectively recruited from 14 memory clinics located in different parts of Sweden. Among these, 1,021 individuals had baseline MMSE scores ranging from 10 to 26, indicating mild-to-moderate AD, and were included in the present study.

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All patients and/or caregivers gave their written informed consent for participation in the study, which was conducted according to the principles of the Helsinki Declaration and was approved by the Ethics Committee of Lund University, Sweden.

The SATS participants were assessed in a structured follow-up program, which evaluated cognition, global rating, instrumental and basic ADL, and the use of community-based service (home help service and adult day care) immediately before the start of ChEI treatment and then every 6 months for 3 years. The ChEI dose was documented after 2 months of therapy and semiannually after baseline. Nurses trained in dementia disorders assessed ADL performance and the amount of service used per week from an interview with the caregiver. After inclusion and baseline assessments, the patients were prescribed ChEIs in accordance with the approved product recommendations. The choice of drug agent and all decisions regarding dosage for the individual patient were left entirely up to the discretion and professional judgment of the dementia specialists, as in routine clinical practice. Medications other than ChEI were allowed, with the exception of memantine, and were recorded at baseline. If memantine was initiated, the individual dropped out from the SATS at that time point.

Using the 12-digit personal identity number assigned to each resident of Sweden, all SATS participants were investigated with the help of the Swedish population register (Swedish Tax Agency) to determine whether they were still alive on December 31, 2013. If not, the date of death was documented.

Assessment Scales

Cognitive ability was evaluated with the MMSE scale that ranges from 0 to 30, in which a lower score indicates more impaired cognition, and the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog; 0–70 points) [23], in which a lower score indicates higher cognitive status. Functional capacity was assessed using the Instrumental Activities of Daily Living (IADL) scale [24], which consists of 8 items: telephone use, shopping, food preparation, housekeeping, doing laundry, mode of transportation, responsibility for own medications, and handling finances. Severity was scored for each item from 1 (no impairment) to 3–5 (severe impairment), giving a total range of 8–31 points. The Physical Self-Maintenance Scale (PSMS) [24] consists of 6 different items: toilet, feeding, dressing, grooming, physical ambulation, and bathing. Each item was scored from 1 (no impairment) to 5 (severe impairment), allowing a total range of 6–30 points. To facilitate comparisons between the MMSE, ADAS-cog, IADL, and PSMS scales, changes in the scores calculated as positive values should be interpreted as indicating improvement, and those calculated as negative values interpreted as indicating decline.

Statistical Analyses

The Statistical Package for Social Sciences (SPSS) software (version 22.0; IBM Corporation, Armonk, N.Y., USA) was used to conduct the statistical analyses. The level of significance was defined as $p < 0.05$, unless otherwise specified, and all tests were two-tailed. Parametric tests were used because of the approximately normally distributed continuous variables and the large sample size. A one-way analysis of variance (ANOVA) was conducted to compare the differences between the means obtained for three or more independent groups, i.e. based on the duration of ChEI treatment. A t test was used to analyze two independent groups, such as deceased participants versus those who were still alive, patients who received a high versus low dose of ChEI, and users versus nonusers of community-based services. A χ^2 test was used to analyze categorical variables, e.g. sex, solitary living, and usage of specific medications. Pearson's correlation coefficient was calculated to investigate the existence of any linear associations between disease severity and ChEI dose. Kaplan-Meier graphs were used to show the differences in time to death. The distribution of time was compared using a log-rank test.

Univariate Cox proportional hazards models were used to estimate separately the effects of different risk factors on the relative risk of time to death. The dependent variable was the length of life (in years) after the start of ChEI treatment. The individuals who were still alive were censored, which implies that they contributed information until December 31, 2013. The analyses were conducted with adjustment for potential confounding of the baseline demographic variables sex and age. Backward stepwise elimination Cox regression models were used (1) to simultaneously estimate the effect of all the potential predictors mentioned below on the time to death, and (2) to explore the effect of community-based services use on time to death by adding those factors to the first model. Variables with $p > 0.05$ were removed from the stepwise models. No violation of the assumption of proportional hazards was detected.

Table 1. Sociodemographic and clinical characteristics (n = 1,021)

Variable	Deceased (n = 841; 82%)	Still alive (n = 180; 18%)	p
Female sex	525 (62)	129 (72)	0.021
APOE ε4 carrier (n = 999)	543 (66)	136 (76)	0.008
Solitary living at baseline	299 (36)	56 (31)	0.264
Completion rate after 3 years	279 (33)	97 (54)	<0.001
Antihypertensives/cardiac therapy	355 (42)	59 (33)	0.019
Antidiabetics	43 (5)	7 (4)	0.573
Asthma medication	38 (5)	6 (3)	0.685
Thyroid therapy	72 (9)	13 (7)	0.656
Lipid-lowering agents	87 (10)	31 (17)	0.014
Estrogens	58 (7)	11 (6)	0.870
NSAIDs/acetylsalicylic acid	260 (31)	45 (25)	0.127
Antidepressants	213 (25)	44 (24)	0.850
Antipsychotics	43 (5)	4 (2)	0.116
Anxiolytics/sedatives/hypnotics	123 (15)	25 (14)	0.907
Estimated age at onset, years	72.9±6.9	68.8±8.4	<0.001
Estimated duration of AD at baseline, years	3.1±2.0	3.0±2.4	0.638
Age at first assessment, years	76.0±6.5	71.7±8.1	<0.001
Education, years	9.4±2.5	9.8±2.8	0.055
Age at death, years	82.0±6.6	n.a.	n.a.
MMSE score at baseline	21.1±3.8	22.9±2.9	<0.001
ADAS-cog score (0–70) at baseline	21.7±9.0	16.4±7.1	<0.001
IADL score at baseline	16.6±5.4	13.0±4.6	<0.001
PSMS score at baseline	7.7±2.4	6.7±1.3	<0.001
Number of concomitant medications at baseline	3.1±2.4	2.4±2.3	0.001
Length in the SATS, months	22.4±13.0	26.7±12.7	<0.001
Mean dose of ChEI during the follow-up period			
Donepezil (n = 518)	6.8±1.8 (2.8–9.4)	7.3±1.7 (3.8–9.4)	0.115
Rivastigmine (n = 212)	5.9±2.1 (2.3–10.5)	7.0±2.0 (3.0–10.3)	0.007
Galantamine (n = 291)	15.0±3.7 (8.0–22.0)	15.6±3.7 (8.0–22.0)	0.186

Values are presented as n (%) or means ± SD (range). n.a. = Not applicable; NSAIDs = nonsteroidal anti-inflammatory drugs.

Predictors

Classical risk factors such as sex, age at baseline, the clinician's estimation of age at onset, years of education, number of apolipoprotein E (APOE) ε4 alleles, and solitary living (no/yes) were included in the first Cox regression model. Measures of AD severity and progression, i.e. cognitive (ADAS-cog score only because of its strong linear correlation with the MMSE), instrumental, and basic ADL abilities at baseline and their rates of change/year, were also included as independent variables. Comorbidity was investigated using the number of concomitant medications at baseline as a potential predictor, as well as the presence of specific medications (no/yes for each group): antihypertensive/cardiac therapy, antidiabetic drugs, asthma medication, thyroid therapy, lipid-lowering agents, estrogens, nonsteroidal anti-inflammatory drugs/acetylsalicylic acid, antidepressants, antipsychotics, and anxiolytics/sedatives/hypnotics. The impact of ChEI therapy during the SATS was analyzed by including the different drug agents (coded as dummy variables), ChEI dose, and treatment duration (in months) in the model.

In a second Cox regression model, together with the above-mentioned variables, use of home help services (hours/week) and adult day care (days/week) at baseline, and annual changes in the amount of these types of care were included as measures of resource use. The change in score (ADAS-cog, IADL, and PSMS) or in the volume of services/week from the baseline to the individual's last assessment was divided by the number of months between these assessments, and multiplied by 12. Most participants did not receive community-based service at baseline; therefore, these potential predictors were treated as categorical variables because of their skewed distributions.

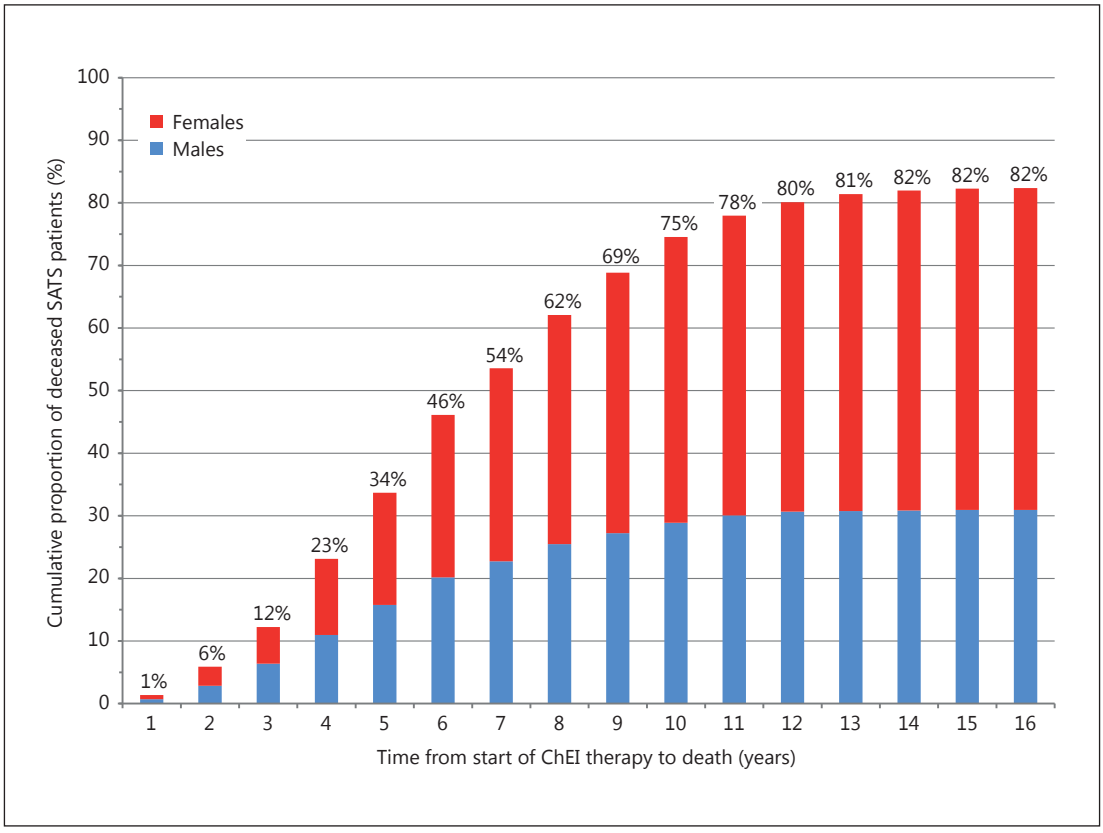

Fig. 1. The cumulative proportion of deceased SATS participants (n = 1,021) by sex, per year after start of ChEI treatment (approximately the time of AD diagnosis) over a follow-up period of up to 16 years. Year 1 indicates a lifespan after baseline of up to 1 year, year 2 indicates >1 to ≤2 years, year 3 indicates >2 to ≤3 years, etc.

The ChEI dose could vary during the treatment period for an individual patient and between patients. Therefore, the mean dose used during the entire follow-up period was calculated for each individual. Moreover, to obtain a similar metric of maximum dosage percentage for the three ChEI agents, the mean dose was divided by the maximum recommended dose for each drug agent, i.e. 10 mg donepezil, 12 mg rivastigmine (oral therapy), and 24 mg galantamine.

Results

Baseline Characteristics according to Death Status

The sociodemographic and clinical characteristics of the 1,021 SATS participants were divided into two groups, deceased up until December 31, 2013 (n = 841, 82%), and still alive (n = 180, 18%), and are displayed in table 1. Figure 1 illustrates the cumulative proportion of deceased men and women per year after the start of ChEI treatment (approximately the time of AD diagnosis) over a follow-up period of up to 16 years.

The proportions of women and of APOE ε4 carriers were significantly lower in the deceased AD group. The 3-year completion rate was higher, and the mean time of participation in the study was longer for those still alive than for the deceased participants. A larger proportion of the deceased group used antihypertensives/cardiac therapy, whereas the use of lipid-lowering agents was more frequent in patients still alive. The deceased participants

Table 2. Cox proportional hazards modelling of time to death (n = 1,021)

	Univariate[a]		Multivariate 1[b], significant predictors		Multivariate 2[c], significant predictors	
	hazard ratio (95% CI)	p	hazard ratio (95% CI)	p	hazard ratio (95% CI)	p
Sex (male = 0, female = 1)	0.67 (0.58–0.77)	<0.001	0.59 (0.51–0.69)	<0.001	0.56 (0.48–0.65)	<0.001
Carrier of APOE ε4 alleles[d]						
1 ε4 allele	0.98 (0.84–1.15)	0.839				
2 ε4 alleles	1.00 (0.80–1.25)	0.996				
Solitary living at baseline (no = 0, yes = 1)	1.11 (0.95–1.30)	0.181				
Antihypertensives/cardiac therapy (no = 0, yes = 1)	1.20 (1.04–1.38)	0.010				
Antidiabetics (no = 0, yes = 1)	1.59 (1.16–2.16)	0.003	1.49 (1.05–2.12)	0.026	1.59 (1.11–2.26)	0.011
Asthma medication (no = 0, yes = 1)	1.19 (0.86–1.65)	0.289				
Thyroid therapy (no = 0, yes = 1)	1.03 (0.81–1.31)	0.818				
Lipid-lowering agents (no = 0, yes = 1)	0.91 (0.73–1.14)	0.411	0.71 (0.55–0.92)	0.009	0.73 (0.56–0.95)	0.017
Estrogens (no = 0, yes = 1)	1.17 (0.89–1.54)	0.265				
NSAIDs/acetylsalicylic acid (no = 0, yes = 1)	1.13 (0.97–1.31)	0.116				
Antidepressants (no = 0, yes = 1)	1.10 (0.94–1.29)	0.228				
Antipsychotics (no = 0, yes = 1)	1.39 (1.02–1.89)	0.037				
Anxiolytics/sedatives/hypnotics (no = 0, yes = 1)	0.97 (0.80–1.18)	0.755	0.75 (0.61–0.94)	0.012	0.78 (0.63–0.97)	0.027
Estimated age at onset (years)	1.00 (0.97–1.03)	0.946				
Age at first assessment (years)	1.06 (1.04–1.07)	<0.001	1.05 (1.04–1.06)	<0.001	1.05 (1.04–1.06)	<0.001
Education (years)	1.00 (0.97–1.03)	0.958				
MMSE score at baseline	0.94 (0.92–0.95)	<0.001	n.a.		n.a.	
ADAS-cog score (0–70) at baseline	1.03 (1.02–1.04)	<0.001	1.03 (1.02–1.03)	<0.001	1.03 (1.02–1.03)	<0.001
IADL score at baseline	1.05 (1.03–1.06)	<0.001				
PSMS score at baseline	1.09 (1.06–1.12)	<0.001				
Number of concomitant medications at baseline	1.07 (1.04–1.09)	<0.001	1.09 (1.06–1.13)	<0.001	1.08 (1.05–1.12)	<0.001
Length of ChEI treatment in the SATS (months)	0.98 (0.97–0.98)	<0.001	0.98 (0.98–0.99)	<0.001	0.98 (0.97–0.99)	<0.001
ChEI dose[e]	0.992 (0.988–0.996)	<0.001	0.995 (0.990–0.999)	0.014	0.995 (0.991–0.999)	0.028
Type of ChEI[f]						
Rivastigmine	0.91 (0.76–1.08)	0.286				
Galantamine	0.74 (0.62–0.88)	0.001				
MMSE score (rate of change per year)	0.98 (0.97–0.99)	<0.001	n.a.		n.a.	
ADAS-cog score (rate of change per year)	0.97 (0.97–0.98)	<0.001	0.99 (0.98–0.99)	0.002	0.99 (0.98–0.99)	0.006
IADL score (rate of change per year)	0.94 (0.93–0.96)	<0.001				
PSMS score (rate of change per year)	0.88 (0.85–0.90)	<0.001	0.92 (0.89–0.95)	<0.001	0.93 (0.90–0.96)	<0.001
Home help service at baseline, h/week[g]			n.a.			
0.50 – 2.00 (n = 56)	1.51 (1.13–2.01)	0.005				
2.25 – 6.00 (n = 49)	1.42 (1.04–1.94)	0.028				
≥6.25 (n = 59)	1.40 (1.07–1.85)	0.016				
Adult day care at baseline, days/week[g]			n.a.			
1 – 2 (n = 30)	1.49 (1.02–2.18)	0.038				
≥3 (n = 17)	1.67 (1.03–2.70)	0.038				
Home help service, increase in h/week per year[g]			n.a.			
0.25 – 2.00 (n = 110)	0.83 (0.66–1.04)	0.112			0.91 (0.72–1.16)	0.453
2.25 – 5.00 (n = 96)	1.42 (1.13–1.79)	0.002			1.33 (1.03–1.72)	0.030
≥5.25 (n = 79)	1.53 (1.19–1.97)	0.001			1.34 (1.02–1.75)	0.034
Adult day care, increase in days/week per year[g]			n.a.			
≤1 (n = 100)	0.91 (0.73–1.15)	0.448			1.09 (0.85–1.40)	0.500
>1 (n = 115)	1.56 (1.27–1.92)	<0.001			1.44 (1.15–1.79)	0.001

Hazard ratios are expressed per 1 unit increase for continuous variables and for the condition present in categorical variables. n.a. = Not applicable; NSAIDs = nonsteroidal anti-inflammatory drugs. [a] Adjusted (if applicable) for the baseline variables sex and age. [b] Model 1, excluding service use terms. [c] Model 2, including community-based service use terms. [d] Noncarrier of APOE ε4 alleles was the reference category. [e] Mean percentage of the maximum recommended dose, i.e. 10 mg for donepezil, 12 mg for rivastigmine, and 24 mg for galantamine. [f] Donepezil was the reference category. [g] 0 h/days per week was the reference category.

were older at the onset of AD and at baseline, had worse cognitive and functional impairment, and received more concomitant medications compared with those still alive. The mean dose of rivastigmine during the study was significantly lower for the deceased patients, whereas the doses of donepezil and galantamine were similar in the two groups. No significant linear associations between cognitive, IADL, or basic ADL abilities at baseline and the mean dose of ChEI during the study were found.

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Cox Regression Models

Univariate Cox proportional hazards modeling showed several risk factors to be related to mortality. Shorter time from AD diagnosis to death was associated with male sex, antihypertensive/cardiac, antidiabetic or antipsychotic therapy, older age, lower cognitive and functional status at baseline or a faster rate of decline, a greater number of concomitant medications, shorter duration of ChEI exposure in the study, a lower dose of ChEI, and treatment with donepezil or rivastigmine. The hazard ratios with 95% confidence intervals (CI) and p values for these variables are listed in table 2. Disease severity at the start of therapy differed between the three ChEI groups; the participants treated with galantamine were less impaired. After adjusting for baseline ADAS-cog and IADL scores in the Cox univariate type of ChEI model, no significant difference in life expectancy among patients treated with specific drugs was found (p = 0.263).

When subjected to multivariate backward elimination modeling, 11 variables from the univariate analyses excluding service use terms were retained in the Cox model of shorter survival time. These variables were: male sex, usage of antidiabetics, older age, more cognitive impairment at the start of ChEI therapy, faster rate of cognitive and basic ADL deterioration, more concomitant medications, shorter duration of ChEI treatment in the SATS, and a lower ChEI dose. Moreover, usage of anxiolytics/sedatives/hypnotics and lipid-lowering agents independently predicted longer lifespan. The coefficients, hazard ratios with 95% CI, and p values for the significant predictors are described in table 2, model 1.

Dose of ChEI

A higher ChEI dose was an independent predictor of increased life expectancy in the multivariate Cox models. The frequency of death over the first 3 years after baseline was lower among individuals who received a higher dose compared with a lower dose during the study [9 vs. 18%; $\chi^2(1) = 16.37$, $p < 0.001$], regardless of drug agent. After up to 16 years of follow-up, the corresponding percentages were 79 versus 86% [$\chi^2(1) = 7.94$, $p = 0.005$]. The individuals who received a higher dose of ChEI had a longer mean ± standard deviation (SD) survival time than those who received a lower dose (6.4 ± 2.9 vs. 5.5 ± 2.8 years; $t_{839} = -4.73$, $p < 0.001$). The median cutoff values for dose were: donepezil, 6.9 mg; rivastigmine, 6.0 mg, and galantamine, 15.0 mg.

Rate of AD Progression

The participants were divided into three groups based on their average speed of cognitive decline in ADAS-cog score/year: ≤0 points (n = 342), >0 to <4 points (n = 300), and ≥4 points (n = 321); 58 patients had one assessment only (at baseline). Figure 2a shows the Kaplan-Meier graph of the distribution of time from the start of ChEI treatment (shortly after AD diagnosis) to death. The log-rank test showed a significantly shorter lifespan for those with the highest progression rate compared with the other two groups (p < 0.001). The individuals were also divided into three groups according to their mean rate of deterioration in PSMS score/year: ≤0 points (n = 394), >0 to <2 points (n = 321), and ≥2 points (n = 243); 63 participants had one evaluation only. Figure 2b shows the Kaplan-Meier graph of the distribution of time from baseline to death. A log-rank test found a higher mortality for those with the fastest speed of basic ADL progression compared with the other groups (p < 0.001).

Duration of ChEI Treatment

The mean ± SD duration of ChEI therapy in the SATS was 23.2 ± 13.0 months. A longer time of exposure to ChEIs was an independent predictor of increased life expectancy in the multivariate Cox models. Depending on the length of participation in the study, the 1,021 patients were divided into four groups: 3-year completers (n = 376), 2-year completers (n =

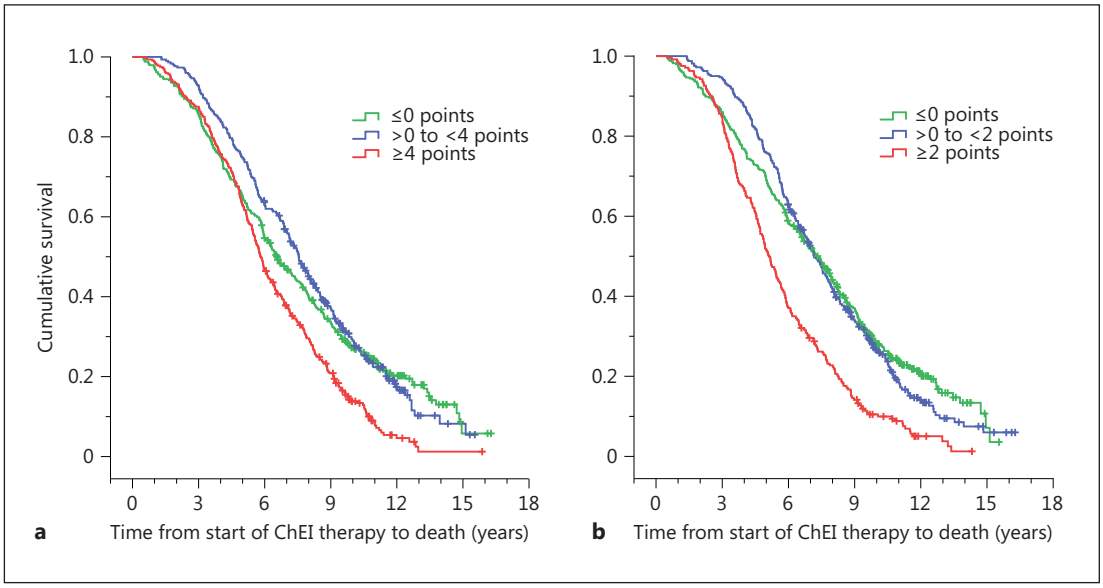

Fig. 2. a Time to death according to rate of progression in cognition. Kaplan-Meier graph of the distribution of time from the start of ChEI therapy (shortly after AD diagnosis) to death for three different groups based on annual mean rate of decline in ADAS-cog score. A log-rank test found significantly shorter survival for those with the fastest progression rate (≥4 ADAS-cog points/year) compared with the other two groups ($p < 0.001$). **b** Time to death according to rate of progression in basic ADL. Kaplan-Meier graph of the distribution of time from the start of ChEI treatment (baseline) to death for three different groups based on the average rate of deterioration in PSMS score per year. A log-rank test found shorter life expectancy for those with the highest speed of progression (≥2 PSMS points/year) compared with the other groups ($p < 0.001$).

211), 1-year completers (n = 222), and 6-month completers (n = 212). Figure 3a shows the Kaplan-Meier graph of the distribution of time from the initiation of ChEI treatment to death for the four groups. The difference in survival among the groups continued to be significant over the follow-up period. The log-rank tests showed differences for all pairwise comparisons, with the exception of the combination of 6-month and 1-year completers after up to 16 years ($p < 0.008$).

Among the 841 deceased individuals, the mean ± SD time from baseline to death was 6.0 ± 2.9 years. The survival time differed between the four groups based on length of ChEI exposure in the SATS: 7.2 ± 2.5 years (3-year completers, n = 279), 6.3 ± 2.9 years (2-year completers, n = 183), 5.0 ± 2.6 years (1-year completers, n = 197), and 4.9 ± 2.9 years (6-month completers, n = 182; $F_{3, 837} = 37.87$, $p < 0.001$). A post hoc test (Bonferroni) showed significant differences for all pairwise comparisons ($p < 0.003$), except for the combination of 6-month and 1-year completers.

Use of Community-Based Services

Home help services at the start of ChEI therapy were used by 152 (18%) of the deceased SATS participants and 12 (7%) of those still alive [$\chi^2(1) = 14.35$, $p < 0.001$]. The mean ± SD hours of home help services used per week were 5.5 ± 4.8; no difference was detected according to death status. Adult day care at baseline was used by 45 (5%) of the deceased patients and 2 (1%) of those still alive, and the mean number of days/week was 2.7 ± 1.4.

Users of any type of community-based services at baseline exhibited shorter mean life expectancy than nonusers (5.2 ± 2.7 vs. 6.2 ± 2.9 years; $t_{839} = 4.15$, $p < 0.001$). Figure 3b

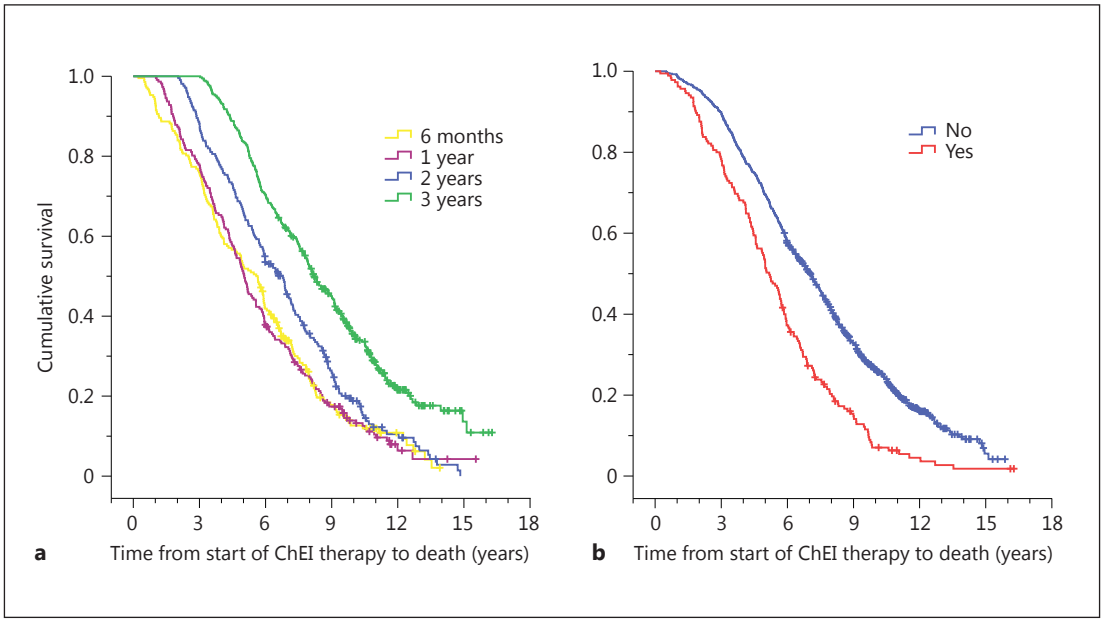

Fig. 3. a Time to death according to duration of ChEI treatment. Kaplan-Meier graph of the distribution of time from the start of ChEI therapy (shortly after AD diagnosis) to death for the four different groups based on length of time in the study. 3 years indicates 3-year completers, 2 years (2-year completers) indicates ≥2 to <3 years, 1 year (1-year completers) indicates ≥1 to <2 years, and 6 months (6-month completers) indicates <1 year. Log-rank tests showed significant differences for all pairwise comparisons ($p < 0.008$) with the exception of the combination of 6-month and 1-year completers. **b** Time to death according to usage of community-based services. Kaplan-Meier graph of the distribution of time from the start of ChEI treatment (baseline) to death for users (yes) and nonusers (no) of the services at baseline. A log-rank test found a significant difference between the two groups ($p < 0.001$).

displays the Kaplan-Meier graph of the distribution of time from the start of ChEI treatment to death for users and nonusers of services at baseline (log-rank test, $p < 0.001$).

In the univariate Cox regression models, use of home help services or adult day care at the initiation of ChEI therapy, regardless of the volume of care, predicted higher mortality. A weekly increase of >2 h of home help service or >1 day of adult day care per year was associated with a shorter lifespan in both the univariate (table 2) and multivariate models (table 2, model 2).

Discussion

This longitudinal AD study performed in a routine clinical setting showed that longer survival time was independently related to a slower rate of decline in cognitive or basic ADL abilities (but not in IADL), a higher dose of ChEI, or longer treatment duration in the SATS, use of anxiolytics/sedatives/hypnotics, or lipid-lowering agents, but not antidiabetic therapy. The risk factors male sex, older age, lower cognitive status, and more concomitant medications were significant predictors of higher mortality, suggesting accuracy of the Cox regression models. Users of community-based services at baseline had a 1 year shorter mean life expectancy than nonusers. A weekly increase of >2 h of home help service or >1 day of adult day care per year was also associated with an earlier death.

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In the present study, the percentage of deceased individuals after 4 years (23%) was the same as in a French mild-to-moderate ChEI-treated AD cohort [25], but higher than the 17% observed in the untreated CERAD patients from the USA [26]. However, the American cohort was considerably younger and better educated than the European cohorts. A recent 2-year randomized placebo-controlled trial reported lower mortality in a galantamine-treated group compared with placebo (3.2 vs. 5.5%) [27]. In the SATS, 5.9% of the individuals had died after 2 years, but their mean age at the start of ChEI therapy was 3 years older. Long-term observational AD studies in clinical practice, controlling for several patient characteristics, have reported conflicting results regarding whether the use of ChEIs prolonged life [14, 15]. The participants in the study by Zhu et al. [15] were, on average, 3 years older and had better cognitive ability at the initiation of ChEI treatment, which might have stronger effects on survival. It is not possible to conclude whether the proportion of deaths over a longer time differs between ChEI-treated and untreated patients based on these mixed findings.

A faster rate of decline of cognitive and basic ADL capacities, but not IADL, predicted higher mortality in this study. Progression in IADL tasks might have less influence on survival compared with the consequences of loss of essential functions during the later stages of AD [28]. Studies of untreated individuals with AD showed that a ≥5-point deterioration in MMSE score after 1 year of follow-up was related to 30–60% increased risk of death [29, 30]. In predominantly ChEI-treated participants, every 1-point increase on the PSMS scale was associated with a 10% increased risk of death/year [17], which was similar to the 8% observed in the SATS. A measure of preprogression rate, based on the patient's initial MMSE score, was also significant in that AD study, but IADL was not addressed [17]. Slow preprogressors measured by MMSE score had a longer survival time than rapid preprogressors; however, whether the effect of ChEI differed by progression group was not investigated [31]. We reported recently that individuals who improved or were unchanged in cognitive or functional performance after 6 months of ChEI therapy lived significantly longer than those who worsened [18]. These findings suggest that patients who experience an initial faster decline or do not respond positively to ChEIs will have a more malignant course of AD and a shorter life expectancy.

In the present study, a longer treatment duration with ChEIs or a higher dose implied lower mortality after adjusting for many demographic and clinical variables. The mean dose of rivastigmine was significantly lower in the deceased SATS cohort, whereas it was similar between the participants who were still alive and the deceased individuals for the other two ChEI agents used. One explanation for this observation is that the frail patients with more advanced AD included in the deceased group had difficulties in tolerating higher doses of oral rivastigmine therapy because of more pronounced gastrointestinal side effects [32]. Few previous AD studies have investigated the potential relationship between time on ChEIs and survival. An older study from our group found no difference in survival between participants who received tacrine treatment for ≥1 versus <1 year. However, the sample size was notably smaller (n = 50, 26 deaths) and the follow-up period shorter (5–6 years) than in the SATS, which might have affected detection of possible differences [16]. Cumulative ChEI and/or memantine use did not affect mortality in another longitudinal observational study of AD patients [17]. The periods of drug exposure were summarized and determined from the onset of symptoms in that study, i.e. the participants could have been treated before the first clinic visit. By contrast, the baseline in the SATS was the start of ChEI therapy, and all patients received continuous treatment. When comparing different studies, it may be important to consider the point when ChEIs were initiated because the first months of positive response after initiation could imply a more favorable outcome over time and longer life expectancy [18].

Treatment with ChEI might also have effects beyond the central nervous system, such as regulation of the immune response, which could influence survival time. For example, inhi-

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bition of acetylcholinesterase in the brain has been reported to suppress systemic inflammation [33]. A recent AD study from our group found that neuroinflammation was an important independent pathology for shorter lifespan [34]. Moreover, the predominant cause of coronary artery disease, atherosclerosis, has been suggested to be an inflammatory disease [35]. Another study observed that ChEI use was related to a decreased risk of myocardial infarction and death; higher ChEI doses increased this association [36]. These studies indicate that potential anti-inflammatory effects of ChEI might be one explanation for the lower mortality rate. The current study is in line with the findings of Nordstrom et al. [36] that ChEI therapy might prolong life expectancy, especially for a subgroup of AD patients with good tolerance of higher dosages and with longer duration of treatment.

Comorbidity and concomitant medications are common in older people and complicate analyses of the direct impact of AD on mortality [37]. Antidiabetic drugs implied a 50–60% increased risk of death in the SATS, whereas antihypertensive/cardiac therapy was an independent significant predictor in the univariate, but not multivariate, Cox models. Previous AD studies reported that diabetes implied even greater (87–99%) risk of death and that some cardiovascular diseases also reduced life expectancy. However, the type of vascular disease (e.g. hypertension) that significantly affected survival differed between the studies [30, 38]. In the present study, lipid-lowering agents and anxiolytics/sedatives/hypnotics were independent predictors of a longer lifespan. Besides the prevention of atherosclerosis, lipid-lowering agents have been shown to reduce mortality in several observational studies of, e.g., various types of heart failure, chronic obstructive pulmonary disease, and sepsis; however, the results are not conclusive [39]. Furthermore, sleep disturbances were independent predictors of cognitive deterioration, behavioral symptoms, falls, and shorter survival in older populations of nondemented and demented individuals. Careful treatment of sleep disturbances might decrease these negative outcomes [40, 41]. Sleep has also been suggested to facilitate clearance of potentially toxic proteins, such as β-amyloid, from the brain. Future studies are needed to determine whether sleep disturbances accelerate AD pathology [42].

Users of community-based services showed a shorter life expectancy than nonusers in the present study. Use of home health services has been strongly associated with impairment in ADL, but not in cognition, among care recipients with AD [43] and thus might serve as an indicator of a loss of functional capacities, an important predictor of increased mortality in dementia [44, 45]. Consistently, we observed that deterioration in basic ADL was an independent predictor of shorter survival in the multivariate models. One study of AD patients from our group made the alarming finding that lower cognitive ability predicted fewer hours of home help service, while worse IADL performance implied a greater amount of help [12]. These findings suggest that community-based services may meet the needs of individuals by helping them with their ADL deficits but not their cognitive impairment.

The strengths of the large-sample naturalistic SATS cohort are the prospective, well-structured evaluations of different aspects of the course of AD after start of ChEI therapy. The Swedish health care system is publicly funded for residents, and the amount of service use is based on the care recipient's needs, i.e. not dependent on their financial situation or insurance coverage [46], which suggests that the SATS participants are representative of the general population. A limitation of the present study is that it is not placebo controlled because of ethical concerns, or randomized according to ChEI agent like other long-term observational studies. Specialists in dementia disorders decided on the ChEI agent and the dose to be administered to each individual patient, in accordance with the standards used in routine clinical practice. Disease severity was not related to the amount of ChEI received during the SATS. It was not possible to determine whether the participants continued ChEI therapy after they had left the study. However, according to general clinical practice in Sweden, we assume that the AD patients who tolerated ChEI well and exhibited positive effects continued with the

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treatment. Discontinuation of ChEI therapy after the study was probably more frequent for those with rapid worsening and/or who were admitted to nursing homes. Health-related events, such as somatic illnesses and disabilities, in the individual's life after the last follow-up may have affected time to death. However, our findings that life expectancy was significantly increased for patients who received higher ChEI doses or were treated for a longer time were observed after the first 3 years, and the group trajectories followed this pattern over subsequent years. Moreover, the multivariate Cox regression models were adjusted for sex, age, cognitive and functional impairment, and concomitant medications, which are factors that are commonly related to mortality.

Very few studies have analyzed the relationships between the duration of ChEI treatment, the occurrence of medical conditions, and survival after diagnosis of AD, and as findings are not consistent, additional studies are warranted. The potential effect of ChEI on the immune system, and other comorbidities such as myocardial infarction and other cardiovascular disorders, needs further investigation.

In conclusion, this observational AD study over 16 years showed that a longer survival time can be expected for individuals who receive and tolerate higher ChEI doses and a longer duration of continuous treatment; thus, no long-term toxicity of ChEIs was demonstrated. Moreover, faster progression in cognitive or basic ADL capacity that reflects the speed of neurodegeneration and loss of essential functions independently predicted a shorter survival, together with male sex, older age, and more concomitant medications, which indicates the accuracy of our statistical models. In particular, antidiabetic therapy was a strong predictor of early death in AD. Use of community-based services might predict higher mortality, especially for those who receive a weekly increase of >2 h of home help service or >1 day of adult day care per year. The measures in the present study can aid the detection of features associated with prognosis for survival of patients with AD typically seen in clinical practice.

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Disclosure Statement

The authors have no disclosures to report.

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