The use of cholinesterase inhibitors and the risk of myocardial infarction and death: a nationwide cohort study in subjects with Alzheimer’s disease

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Aims
Cholinesterase inhibitors (ChEIs) are used for symptomatic treatment of Alzheimer’s disease. These drugs have vago-tonic and anti-inflammatory properties that could be of interest also with respect to cardiovascular disease. This study evaluated the use of ChEIs and the later risk of myocardial infarction and death.

Methods and results
The cohort consisted of 7073 subjects (mean age 79 years) from the Swedish Dementia Registry with the diagnoses of Alzheimer’s dementia or Alzheimer’s mixed dementia since 2007. Cholinesterase inhibitor use was linked to diagnosed myocardial infarctions (MIs) and death using national registers. During a mean follow-up period of 503 (range 0–2009) days, 831 subjects in the cohort suffered MI or died. After adjustment for confounders, subjects who used ChEIs had a 34% lower risk for this composite endpoint during the follow-up than those who did not [hazard ratio (HR) 0.66, 95% confidence interval (CI) 0.56–0.78]. Cholinesterase inhibitor use was also associated with a lower risk of death (HR: 0.64, 95% CI: 0.54–0.76) and MI (HR: 0.62, 95% CI: 0.40–0.95) when analysed separately. Subjects taking the highest recommended ChEI doses (donepezil 10 mg, rivastigmine 6 mg, galantamine 24 mg) had the lowest risk of MI (HR: 0.35, 95% CI: 0.19–0.64), or death (HR: 0.54, 95% CI: 0.43–0.67) compared with those who had never used ChEIs.

Conclusion
Cholinesterase inhibitor use was associated with a reduced risk of MI and death in a nationwide cohort of subjects diagnosed with Alzheimer’s dementia. These associations were stronger with increasing ChEI dose.

Keywords
Choline esterase inhibitors • Myocardial infarction • Alzheimer’s dementia

Introduction
Taken together, the various features of cardiovascular disease (CVD) comprise the leading cause of death worldwide, and the World Health Organization estimated in 2008 that 12.6% of all deaths globally were caused by ischaemic heart disease.1 The estimated global cost of CVD was USD 863 billion in 2010, and this cost is expected to rise by 22% in the next 20 years due to population ageing.2 Although CVD risk factors, such as hypertension, hyperlipidaemia, smoking, and diabetes, are well known and effective drugs are available, the risk of cardiovascular death remains about five-fold greater in individuals with at least two of these risk factors at the age of 55 years than in those with no risk factor.3 These data suggest that the identification of new drugs with modes of action that differ from those of available drugs would be of interest.

Cholinesterase inhibitors (ChEIs) were introduced in the mid-1990s for the treatment of mild-to-moderate Alzheimer’s disease (AD). Three ChEIs (donepezil, rivastigmine, and galantamine) are currently available and have shown similar AD treatment effects in randomized-controlled studies.4 These effects have been attributed to the reduced breakdown of acetylcholine, a neurotransmitter that has been associated with memory function, by the blockade of the enzyme acetylcholinesterase. The side effects are primarily affecting the gastrointestinal system. However, vagotonic side effects could also be of interest with respect to the risk of CVD.4,5 Furthermore, experimental studies in mice and humans have suggested that...
ChEIs also have anti-inflammatory properties.\textsuperscript{6–8} Given that atherosclerosis, which underlies most forms of CVD, is considered to be an inflammatory disease, such effects could be of interest with respect to CVD.

Thus, the present cohort study investigated the association between ChEI use and the later risk of myocardial infarction (MI) and death in a nationwide cohort of \textasciitilde 7000 individuals diagnosed with AD.

**Methods**

**Data source and study population**

Data used in this study were obtained from the Swedish Dementia Registry (SveDem; www.svedem.se), a web-based registry established in 2007 to improve the quality of dementia diagnosis, treatment, and care in Sweden. This incident-based database here represents \textasciitilde 90% of all new dementia diagnoses in memory clinics (n = 53) in Sweden. SveDem lists the age, gender, heredity, body mass index, living conditions, cognitive evaluations using the Mini-Mental State Examination (MMSE),\textsuperscript{9} the content of diagnostic work up, type of dementia diagnosis, drug treatment, and support for each patient by county and municipality.\textsuperscript{10}

A search of SveDem for all patients with newly diagnosed AD (including early-onset, late-onset, and mixed dementia) according to the International Classification of Diseases (ICD) 10 criteria between 1 May 2007 and 31 December 2010 yielded the records of 7073 patients. For these patients, a MMSE was performed in 97.8%, an extended neuropsychological examination was performed in 89.4%, laboratory testing was performed in 96.3%, and a computed tomography scan was performed in 86.9% of the patients, while MRI was performed in an additional 6.5%. The regional human ethics committees in Stockholm and Umeå, and the National Board of Health and Welfare in Sweden approved this study. Data were coded and anonymized before statistical analysis.

**Assessment of cardiovascular disease, death, emigration, and cholinesterase inhibitor use**

Diagnoses and expedited drugs in the cohort at baseline and during the follow-up were identified by searching the Swedish National Patient Register (NPR) and the national register for prescribed and expedited drugs (NDR), administered by the Centre for Epidemiology at the National Board of Health and Welfare in Sweden. By using NPR, we got information about all diagnoses set during inpatient care in Sweden since 1998 and all outpatient care since 2001. The ICD 10 codes I21.xx (MI), I20.xx (angina pectoris), and I63.xx (ischaemic stroke) were used. Through NDR we got information about all drugs prescribed and expedited in Sweden since July 2005. The Anatomical Therapeutic Chemical Classification (ATC)-codes N06DA (ChEIs), N06A (antidepressants), N05A (neuroleptics), C03, C07, C08, C09 (antihypertensive drugs), and A10 (antidiabetic drugs) were used. Diagnoses and expedited drugs, i.e. drugs that were collected by the patient at the pharmacy, were linked to individuals in the cohort using the unique social security number assigned to each Swedish citizen. A validation study of the NPR including 713 patients with diagnosed MIs between 1987 and 1995 determined that 86% of patients fulfilled the present criteria for MI diagnosis, 9% likely had an MI, and the remaining 5% did not have an MI.\textsuperscript{11}

Information on deaths occurring within the cohort during the study period was obtained through record linkage with the NPR. Information about emigration within the cohort was obtained using the Statistics Sweden database.

**Statistical analysis**

Baseline differences in the cohort for continuous variables were investigated using Student’s t-test for independent samples. Differences in the distribution of living conditions between subjects with and without ChEI use were examined using the \( \chi^2 \) test. Associations between ChEI use and the risk of MI and death were investigated using Cox proportional hazard models, with baseline defined as the date of first expedited ChEI dose, or date of dementia diagnosis in subjects who had never used ChEIs. All the models were adjusted for age, gender, mixed dementia, residency, living with co-resident, home care, MMSE score, expedited antidepressants, neuroleptics, antihypertensives, and any history of CVD according to Table 1. The study end of the follow-up for the outcome of MI was the date of emigration, date of MI, date of death, or 31 December 2010, whichever came first. The end of follow-up for the outcome of death was the date of emigration, date of death, or 31 December 2010, whichever came first. Kaplan–Meier curves were used to check proportional hazard assumptions.

The robustness of the results for the outcomes of death and MI was tested in several sensitivity analyses. Since there were relevant differences in many of the variables assessed at baseline for those who used ChEI and the rest of the cohort, the associations between ChEI and the outcomes were tested according to subgroups of different gender, age, previous CVD, cognitive function, use of antihypertensives and diagnosis of mixed dementia at baseline. The robustness of the results was also tested in a matched case–control cohort based on the total study cohort (n = 7073). Each control (never used ChEI) was then matched against one case (used ChEI at least once) based on propensity scores. These scores were derived from the variables gender, age, diagnosis of mixed dementia, cognitive function, residency, living with co-resident, home care, previous MI, stroke and angina pectoris, use of antihypertensives, antidepressants, neuroleptics, and antidiabetic medication at baseline. As shown in Table 1 matching based on these variables gave a case–control cohort with similar background data. The association between ChEI use with the outcomes death and MI was then investigated in this cohort by using Cox proportional hazard models adjusting for the propensity scores. In a final sensitivity analysis, we evaluated whether the associations found were restricted to the use of ChEI or applied also to other drugs used in the treatment of dementia. For these, analyses tested whether memantine was associated with the outcomes death and MI in the total cohort using Cox regression. Memantine is a partial N-methyl-D-aspartate (NMDA) receptor antagonist with the indication moderate-to-severe AD.\textsuperscript{12}

All statistical tests were two-sided and \( P < 0.05 \) was considered significant. The SPSS software with the R essentials application was used for all statistical analyses (ver. 20.0 for PC; SPSS, Inc., Chicago, IL, USA).

**Results**

The study cohort consisted of 7073 men and women with a mean age of 78.9 (range 41–99) years at baseline. Of these subjects, 5159 (72.9%) subjects received expedited ChEIs at least once (Table 1). The mean interval between the first and last time ChEI was expedited was 495 (range 0–2008) days. Compared with the rest of the cohort, these subjects were younger and female, had higher MMSE scores, and lived at home alone with no home care. In addition, fewer of these subjects had a history of CVD than those who had never been prescribed ChEIs. Only 10 subjects were expedited ChEI once. In the matched case–control cohort based on all variables in Table 1, there were marginal differences in the baseline variables between subjects using and not using ChEI.
Use of cholinesterase inhibitors and the risk of MI and death

In those prescribed ChEI at least once (n = 5159), 74 subjects suffered an MI and 427 subjects died during a mean follow-up period of 571 (range 0–2009) days. In the rest of the cohort (n = 1914), 42 subjects suffered an MI and 329 subjects died during a mean follow-up period of 392 (range 2–1333) days. Figure 1 presents cumulative survival curves of the cohort according to occurrence of MI or death during the follow-up, adjusted for the influences of age, gender, mixed dementia, MMSE score, living conditions, history of CVD and use of antidepressants, antihypertensive drugs, antidiabetic, and neuroleptics (all confounders). After adjustment for all confounders, subjects who used ChEIs had a 34% lower risk for the composite outcome of MI or death during the follow-up, adjusted for the propensity scores, the use of ChEI was associated with a decreased risk for the composite outcome of MI or death (P = 0.66; 95% CI: 0.42–0.65; Figure 2). The highest dose of ChEI was also associated with the highest risk reduction for MI (HR: 0.35, 95% CI: 0.19–0.64) and death (HR: 0.54, 95% CI: 0.43–0.67), when evaluated separately, or MI in a cohort with previous CVD (HR: 0.29, 95% CI: 0.09–0.94, Figure 2).

In a first set of sensitivity analyses, the associations between ChEI use and the composite outcome of MI or death remained significant for subgroups according to different gender, age, CVD at baseline, use of hypertensive drugs, mixed dementia, Alzheimer’s dementia, and cognitive function (Table 2). These associations were also similar in the subgroups for the outcome of death and MI when analysed separately (Table 2). Secondly, we analysed ChEI use in the matched case–control cohort. After adjustment for the propensity scores, the use of ChEI was associated with a decreased risk for the composite outcome of MI or death (HR: 0.66, 95% CI: 0.34–0.32; 408582 by guest on 15 March 2019)

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Based on the last date of expedited ChEI, the dose was categorized as low (donepezil 5 mg, rivastigmine 3 mg or less, galantamine 8 mg), moderate (rivastigmine 4.5–6 mg, galantamine 16 mg), or high (donepezil 10 mg, rivastigmine 6 mg or more, galantamine 24 mg). Using subjects who had never been prescribed ChEIs as the reference and adjusting for all confounders, we found that the risk of the composite outcome of MI or death decreased with increasing ChEI dose (P for trend < 0.001), and those receiving the highest ChEI doses had the lowest risk compared with the reference (HR: 0.52, 95% CI: 0.42–0.65; Figure 2). The highest dose of ChEI was also associated with the highest risk reduction for MI (HR: 0.35, 95% CI: 0.19–0.64) and death (HR: 0.54, 95% CI: 0.43–0.67), when evaluated separately, or MI in a cohort with previous CVD (HR: 0.29, 95% CI: 0.09–0.94, Figure 2).

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0.32 – 0.86). In a third set of analyses, the association between memantine, a selective NMDA-receptor antagonist, and the different outcomes was analysed (Table 2). After adjustment for all confounders, the use of memantine \( (n = 1747) \) was not associated with the composite outcome of MI or death (HR: 1.16, 95% CI: 0.97 – 1.38), death (HR: 1.15, 95% CI: 0.95 – 1.38), or MI (HR: 1.22, 95% CI: 0.76 – 1.97) analysed separately (Table 2). Finally, exclusion of all subjects that died within 90 days did only slightly attenuate the associations between ChEI use and the composite outcome of MI or death (HR: 0.71, 95% CI: 0.60 – 0.85), MI (HR: 0.70, 95% CI: 0.45 – 1.10), or death (HR: 0.69, 95% CI: 0.57 – 0.82) in the total cohort after adjustment for all confounder.

**Discussion**

In the present observational study, ChEI use was associated with \( \sim 35\% \) reduced risk of MI or death in a cohort of subjects with diagnosed AD. This risk reduction was similar in subcohorts of subjects according to different age, gender and cognitive function, presence of CVD or not, and diagnosis of Alzheimer’s dementia or Alzheimer’s mixed dementia. This risk reduction was also similar in case–control cohorts that were matched based on all potential confounders. The risk of both MI and death decreased with an increasing dose of ChEI. However, given that this is an observational study, it would be of value if the findings could be confirmed in a randomized controlled trial.
To our knowledge, no previous clinical study has linked the use of ChEIs to a reduced risk of CVD in general or MI in particular. Furthermore, the incidence of MIs has not been reported in high-quality randomized controlled trials with durations of at least 5 months investigating the effects of ChEIs in subjects with AD.13–24 The small numbers of participants and relatively short follow-up periods (1 year or more in only two trials) in these trials may have resulted in the absence of CVD in these studies.18,19 Because MIs are rare, pooling of safety data from previous randomized controlled studies would be necessary to create a sufficiently large cohort. Such an effort could be of great value, given the results of the present observational study.

The survival curve for MI or death in the present study cohort indicates that the treatment effects associated with ChEIs may appear in the early stages following onset use. This early effect could admittedly be related to the possibility that ChEI treatment was not typically considered in AD subjects with CVD. For this reason, the primary analysis was adjusted for previous CVD and one of the sensitivity analyses examined a subcohort of subjects with known CVD at baseline. The risk reduction associated with ChEI use was similar in both cohorts, although the estimated treatment effects only reached statistical significance for the highest ChEI doses in the subcohort with previous CVD.

Given that CVD is the major cause of death in Sweden and worldwide,1 we also tested the hypothesis that ChEI use was related to a reduced risk of death in subjects with AD. In the primary analysis, ChEI use was associated with a reduced risk of death of approximately 35%, as for MI. This result should be interpreted with caution, given the risk that critically ill patients are not typically prescribed ChEIs at the time of diagnosis. However, the exclusion of subjects that died within 3 months attenuated the treatment effect results with respect to death only slightly. As for MIs, the treatment effect with respect to death increased with higher ChEI doses.

Since the study design of the present study was observational, we can only speculate about the mechanisms of action underlying the cardiovascular effects found. It is of interest that atherosclerosis, which underlies most MIs, is considered to be an inflammatory disease.25 Within the atherosclerotic plaque immune cells produce cytokines that decreases the stability of the plaque, increasing the risk of plaque rupture, and a subsequent MI. Therefore, the documentation of anti-inflammatory properties of ChEIs due to reduced acetylcholine breakdown is of interest.26–28 Treatment with ChEIs has been shown to reduce peripheral cytokine production in experimental studies28 and in humans.2 However, there are also other, and perhaps more likely mechanisms that may contribute to the associations found in the present study. In an experimental model in rats, vagal nerve stimulation after MI resulted in an improved cardiac function and survival.29 In two later studies,29,30 donepezil treatment resulted in favourable effects after MI and reduced atherosclerosis in animal models. In humans, ChEI treatment was also associated

### Table 2  Associations between cholinesterase inhibitor use at baseline and the risks of myocardial infarction and death during the follow-up

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Composite of MI or death (n = 831)</th>
<th>Death (n = 756)</th>
<th>MI (n = 116)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>Total cohort (n = 7073)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever using ChEI (n = 5159)</td>
<td>0.66 (0.56–0.78)</td>
<td>0.64 (0.54–0.76)</td>
<td>0.62 (0.40–0.95)</td>
</tr>
<tr>
<td>Ever using memantine (n = 1747)</td>
<td>1.16 (0.97–1.38)</td>
<td>1.15 (0.95–1.38)</td>
<td>1.22 (0.76–1.97)</td>
</tr>
<tr>
<td>Subgroup analyses based on ever using ChEI</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Female gender (n = 4482)</td>
<td>0.67 (0.53–0.83)</td>
<td>0.62 (0.49–0.78)</td>
<td>0.68 (0.39–1.17)</td>
</tr>
<tr>
<td>Male gender (n = 2591)</td>
<td>0.65 (0.51–0.83)</td>
<td>0.65 (0.50–0.84)</td>
<td>0.58 (0.29–1.15)</td>
</tr>
<tr>
<td>Age &lt; 80 years (n = 3584)</td>
<td>0.53 (0.38–0.72)</td>
<td>0.52 (0.37–0.73)</td>
<td>0.43 (0.20–0.95)</td>
</tr>
<tr>
<td>Age ≥ 80 years (n = 3489)</td>
<td>0.72 (0.60–0.87)</td>
<td>0.69 (0.56–0.84)</td>
<td>0.71 (0.43–1.17)</td>
</tr>
<tr>
<td>CVD at baseline (n = 1251)</td>
<td>0.52 (0.38–0.72)</td>
<td>0.50 (0.36–0.70)</td>
<td>0.61 (0.29–1.28)</td>
</tr>
<tr>
<td>No CVD at baseline (n = 5822)</td>
<td>0.73 (0.60–0.88)</td>
<td>0.69 (0.56–0.86)</td>
<td>0.69 (0.40–1.18)</td>
</tr>
<tr>
<td>Use of anti-hypertensives (n = 4585)</td>
<td>0.69 (0.57–0.83)</td>
<td>0.68 (0.56–0.83)</td>
<td>0.59 (0.37–0.96)</td>
</tr>
<tr>
<td>No anti-hypertensives (n = 2488)</td>
<td>0.56 (0.40–0.79)</td>
<td>0.51 (0.36–0.72)</td>
<td>0.73 (0.28–1.93)</td>
</tr>
<tr>
<td>Mixed-dementia (n = 2696)</td>
<td>0.67 (0.54–0.84)</td>
<td>0.66 (0.52–0.83)</td>
<td>0.57 (0.31–1.07)</td>
</tr>
<tr>
<td>Alzheimer’s disease (n = 4377)</td>
<td>0.55 (0.51–0.83)</td>
<td>0.62 (0.48–0.80)</td>
<td>0.67 (0.37–1.22)</td>
</tr>
<tr>
<td>MMSE-score less than 22 (n = 2978)</td>
<td>0.65 (0.53–0.80)</td>
<td>0.64 (0.51–0.79)</td>
<td>0.55 (0.30–1.02)</td>
</tr>
<tr>
<td>MMSE-score of 22 or more (n = 3665)</td>
<td>0.68 (0.51–0.90)</td>
<td>0.64 (0.47–0.86)</td>
<td>0.69 (0.38–1.27)</td>
</tr>
<tr>
<td>Matched case–control cohort 1:1 (n = 3352) based on ever using ChEIA</td>
<td>0.66 (0.55–0.79)</td>
<td>0.60 (0.50–0.72)</td>
<td>0.52 (0.32–0.86)</td>
</tr>
</tbody>
</table>

Hazard ratios are also presented in separate analyses for subjects according to gender, age at baseline, cardiovascular disease or stroke (CVD) at baseline, use of anti-hypertensive drugs, diagnosis of mixed dementia, and Mini-Mental State Examination (MMSE) score at baseline. In a separate analysis, hazards are presented for ever using memantine. Hazard ratios (HR) and 95% confidence intervals (95% CIs) are presented adjusted all variables in Table 1, except weight and height. Finally, hazards are presented for ever using ChEI in a matched case–control cohort.

*A The propensity scores used for matching were based all variables in Table 1, except weight and height. The hazard ratios presented were adjusted for the propensity scores.
with an increased risk of hospitalization for bradycardia through an increased vagal tone. In contrast, in a recent study negative chronotropic effects of ChEI treatment were not found in subjects recently diagnosed with AD. With respect to our results, effects on the cardiac system from ChEI use, such as those found in some of the studies above, could reduce oxygen demands, improve cardiac function, and thereby reduce the risk of MI and death.

**Limitations**

The major limitation of the present study is its observational design. Marked differences in many examined factors were present at baseline between ChEI users and the rest of the cohort, increasing the risk of confounding by indication. Thus, it is likely that subjects that were generally healthier at baseline would be more often prescribed ChEI, and perhaps also higher doses of ChEI. Therefore, all the analyses were adjusted to correct for these differences, and the results were also similar in the matched case-control cohort. Nevertheless, there could be other confounders, that we did not have access to, that would influence the associations found, e.g. use of statins. Furthermore, although hypothetically, subjects that are prescribed ChEI may be subjected to a more advanced and comprehensive health care concerning their dementia. However, in the present study, the positive treatment effects were restricted to the use of ChEI and did not apply to memantine, a drug that is also prescribed to subjects with Alzheimer’s dementia. In the present study, the diagnoses of MI collected from the Swedish NPR were not validated. However, MI data obtained from NPR have been validated previously, and have shown high sensitivity (94%) and a high positive predictive value (86%). Although the accuracy of dementia diagnoses registered in SveDem has not been validated, this database reports the diagnostic tools used in each case. Furthermore, >95% of patients in this cohort were diagnosed and treated at memory clinics by physicians specializing in dementia disorders. Finally, although there may be cases of misclassification, the treatment effects of ChEI with respect to the outcomes were similar in patients diagnosed with Alzheimer’s dementia and Alzheimer’s mixed dementia.

**Conclusions**

In summary, ChEI use was found to be associated with reduced risks of MI and death in subjects with AD. These associations were stronger with higher ChEI doses. Given that this was an observational study, it would be of value if the results could be confirmed in a study with higher evidence.

**Acknowledgements**

The authors are grateful to the national Swedish Dementia Registry (SveDem, www.svedem.se) for providing data for this study and thank all patients, caregivers, and reporting units for providing information.

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**Conflict of interest:** None declared.

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