

Cardiovascular Outcomes of Cholinesterase Inhibitors in Individuals with Dementia: A Meta-Analysis and Systematic Review

Ahmet Turan Isik, MD,^{*1} Pinar Soysal, MD,^{*1} Brendon Stubbs, PhD,^{†‡§1} Marco Solmi, MD,[¶] Cristina Basso, MD, PhD,^{||} Stefania Maggi, MD, PhD,^{**} Patricia Schofield, PhD,[§] Nicola Veronese, MD,^{||**1} and Christoph Mueller, MD^{†‡1}

OBJECTIVES: To evaluate the cardiovascular (CV) effects of acetylcholinesterase inhibitors (AChEIs) in individuals with dementia

DESIGN: Systematic review and meta-analysis.

SETTING: Two authors independently searched major electronic databases from inception until June 17, 2017, for longitudinal (without a control group) and cohort (with a control group) studies reporting CV outcomes in relation to AChEIs. Randomized controlled trials were excluded because they included relatively healthy subjects.

PARTICIPANTS: Individuals with dementia and controls.

MEASUREMENTS: Changes in CV parameters were summarized using standardized mean differences (SMDs) with 95% confidence intervals (CIs). Event rates were used to assess incidence of hypertension and bradycardia. Incidence of CV events in demented patients versus in healthy controls were compared using hazard ratios (HRs).

RESULTS: Of 4,588 initial hits, 31 studies including 258,540 individuals with dementia and 2,246,592 controls were analyzed. In longitudinal and open-label studies, AChEIs were associated with a significantly greater incidence of hypertension (n=1,573, 4%, 95% CI=2–8%, I²=47%) and bradycardia (n=13,703, 2%, 95% CI=1–6%, I²=98%). AChEIs were associated with a decrease in

heart rate (SMD=−1.77, 95% CI=−3.58–0.03, I²=78%) and an increase in PR interval (SMD=0.10, 95% CI=0.008–0.19, I²=3%) from baseline. During a median follow-up of 116 weeks, AChEIs were associated with a significantly lower risk of CV events (stroke, acute coronary syndrome, CV mortality; HR=0.63, 95% CI=0.45–0.88, I²=18%), without a significantly greater risk of bradycardic events (HR=1.40, 95% CI=0.76–2.59, I²=98%).

CONCLUSION: AChEI therapy may be associated with negative chronotropic and hypertensive effects but also with lower risk of CV events. *J Am Geriatr Soc* 66:1805–1811, 2018.

Key words: acetylcholinesterase inhibitors; bradycardia; hypertension; cardiovascular disease

From the ^{*}Unit for Aging Brain and Dementia, Department of Geriatric Medicine, Faculty of Medicine, Dokuz Eylul University, Izmir, Turkey;

[†]Institute of Psychiatry, Psychology, and Neuroscience, King's College London; [‡]South London and Maudsley National Health Service Foundation Trust, London; [§]Health, Social Care, and Education, Anglia Ruskin University, Chelmsford, United Kingdom; [¶]Department of Neurosciences, University of Padova, Padova; ^{||}Azienda Unità Locale Socio Sanitaria 3, “Serenissima”, Mirano, Italy; and the ^{**}National Research Council, Neuroscience Institute, Aging Branch, Padova.

¹These authors contributed equally to the manuscript.

Address correspondence to Ahmet Turan Isik, MD, Unit for Aging Brain and Dementia, Department of Geriatric Medicine, School of Medicine, Dokuz Eylul University, 35340 Balcova, Izmir, Turkey. E-mail: atisik@yahoo.com

See related Editorial by Holly M. Holmes and Rajender R. Aparasu

DOI: 10.1111/jgs.15415

Acetylcholinesterase inhibitors (AChEIs), including donepezil, rivastigmine, and galantamine, are first-line treatment for dementia in Alzheimer's disease (AD).¹ They are widely used, appear to be well tolerated, and have a beneficial effect on cognitive function.^{1,2} Although the target organ for this group of drugs is the brain, the heart is also rich in cholinesterases, and inhibition of the enzyme may affect cardiac function through vagotonic effects.^{1,2} A number of cholinergic cardiac side effects have been reported,^{2,3} including hypotension, bradycardia, heart block, and QT/QTc prolongation.³ There has been increasing concern among prescribers about the potential for these adverse effects associated with AChEIs, especially in older adults with AD.¹ Conversely, cardioprotective effects of AChEIs have been reported in the literature.⁴ To the best of our knowledge, no systematic review and meta-analysis has considered the complete relationship between AChEIs and cardiac outcomes in people with dementia.

We conducted a systematic review and meta-analysis of observational studies to determine changes in cardiovascular (CV) parameters (blood pressure and electrocardiogram (ECG) parameters) associated with the use of AChEIs in individuals with dementia (primary aim) and to compare how these medications might affect cardiac outcomes in individuals with dementia and controls (secondary aim).

METHODS

This systematic review was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology criteria and the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.^{5,6} The protocol for this systematic review was registered in PROSPERO (https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015032258).

Search Strategy

Two investigators (ATI, PS) independently searched major databases (PubMed, Medline, Scopus, Embase) without language restrictions, from inception until June 17, 2017. An example of the search terms used for PubMed are presented in Supplementary Table S1; similar searches were run in the other databases. The reference lists of the articles included in the analysis were hand searched to identify additional, potentially relevant publications. Conference abstracts were also considered and authors contacted for additional information if needed. Any inconsistencies were resolved by consensus with a third author (CM).

Study Selection

We included studies that reported at least 1 outcome of cardiac safety (defined in Outcomes below) and had one of the 3 designs: longitudinal (without a control group), repeated observations of the outcomes of interest over a follow-up period; open-label (without a control group) trials with a blinded randomization phase and without placebo (e.g., with a group taking another AChEI or a different dose of the same drug); and longitudinal studies with a control group (cohort) that compared people taking AChEIs with a control group. Because of their similar nature, longitudinal and open-label trials were analyzed together because we synthesized data only from participants receiving AChEIs in both studies. In the case of open-label trials—2 groups using AChEIs—were treated as separated groups.

Inclusion and Exclusion Criteria

We considered only studies that had a baseline and follow-up evaluation; included individuals with all types of dementia; included at least one group taking an AChEI, including donepezil, galantamine, and rivastigmine; and reported data on CV parameters and outcomes (ECG and blood pressure) and CV events (onset in people taking

AChEIs), independent of the definition used for these conditions.

Studies were excluded if they reported data on sub-clinical CV events (e.g., carotid atherosclerosis) that could not be separated from the clinical manifestations, were conducted in vitro or in animal models, or were randomized controlled trials, which were excluded because they frequently include selected relatively healthy subjects that do not necessarily reflect the complex clinical presentation of people with dementia^{7,8} and the results cannot be readily applied to real-world populations of people with dementia.”

Data Extraction

Two authors (PS, NV) independently extracted data from the selected studies using a standardized spreadsheet. Any disagreement was resolved with a third author (BS). Information was extracted on characteristics of the study population (e.g., sample size, demographics, setting); type of dementia (AD, vascular dementia, other, mixed) and corresponding criteria used for diagnosis; type of drug and dosage; mean age, percentage of women, and mean baseline Mini-Mental State Examination score according to treatment with AChEI; and duration of follow-up.

Outcomes

The primary outcomes were changes (from baseline to follow-up in those with dementia) in blood pressure, pulse (objective measurement of blood pressure and heart rate), and ECG (PR, QRS, corrected QT intervals) parameters in longitudinal studies. The incidence rate of hypertension (objective measurement or self-reported) and bradycardia (ECG or objective measurement) in assessments of baseline vs follow-up were also considered as primary outcomes.

Secondary outcomes were incidence of new CV events, defined based on physiology of these events as CV events (stroke, acute myocardial infarction, acute coronary syndrome, CV mortality) and bradycardic events (e.g., bradycardia, atrioventricular block, pacemaker insertion) in cohort studies.

Assessment of Study Quality

Two independent reviewers (PS, MS) assessed the quality of studies, with a third available to resolve any discrepancies (BS). The Newcastle-Ottawa Scale (NOS), which assigns a maximum of 9 points based on selection, comparability, and outcome,^{6,9} was used to assess study quality.⁶

Statistical Analysis

The meta-analysis was performed using Comprehensive Meta-Analysis 2.0 software. When combining studies, a random effects model was used to account for study heterogeneity,¹⁰ and data were pooled when 4 or more studies contained the outcome of interest.

We calculated standardized mean differences (SMDs) for studies measuring changes in CV parameters (means and standard deviations) from baseline to follow-up. The

event rate was used to assess the cumulative incidence of hypertension and bradycardia between baseline and follow-up. All estimates were calculated together with 95% CIs. In cohort studies, the incidence of CV events in people taking AChEIs was compared with that of healthy controls using hazard ratios (HRs), most of which were adjusted for potential confounders.

Study heterogeneity was measured using the chi-square and I-square statistics, assuming that $p < .05$ for the former and a value of 50% or greater for the latter indicated significant heterogeneity.¹⁰ We conducted a pre-planned metaregression analysis to see whether some variables, including continent in which the study was conducted (North America, Europe, Asia), type of drug (donepezil, galantamine, rivastigmine), type of dementia (AD, othe), follow-up duration (divided into $<$ vs 24 weeks) could affect blood pressure and ECG results. In studies using a control group, an outlier study reporting findings contrary to those of the others was removed in a sensitivity analysis.

Publication bias was assessed by visually inspecting funnel plots and using the Begg-Mazumdar Kendall tau and Egger bias tests.^{11,12} Then, to account for publication bias, we used the trim-and-fill method, which adjusts for the potential effect of unpublished (imputed) studies.¹¹ Finally, we calculated the classic fail-safe number (the number of missing studies that would bring the p -value to the alpha).

RESULTS

The search identified 4,588 nonduplicated potentially eligible studies. After excluding 4,324 papers after title and abstract review, 264 full-text articles were examined, and 31 studies were included in the systematic review with meta-analysis (22 longitudinal studies without a control group; 9 cohort studies with a control group) (Supplementary Figure S1). Seven of those were open-label studies.^{20–24,33,37} The 22 longitudinal studies included a total of 34 independent cohorts.

Study and Participant Characteristics

Study and participant characteristics are summarized in Supplementary Table S2 (longitudinal studies) and Supplementary Table S3 (cohort studies). Altogether, the 31 studies analyzed represented 258,540 individuals with dementia (15,041 in longitudinal studies, 243,499 in cohort studies) and 2,246,592 controls.^{13–34} Approximately one-third of the participants had AD, and 66.4% had mixed dementia (Supplementary Tables S2 and S3).

Longitudinal Studies Reporting on Changes Over Time in CV Outcomes

The 34 cohorts across the 22 articles included 15,041 participants with dementia. These studies were mainly conducted in Europe (16 cohorts), in community-dwellers (18 cohorts), and in participants with AD (29 cohorts). The 15,041 participants had a mean age of 75.8 ± 7.1 and a baseline mean Mini-Mental State Examination score of

18.0 ± 4.7 , indicating a moderate level of cognitive impairment, and 58.5% were female (6, 15–35) (Supplementary Table S2). The quality of these studies was generally sufficient (median NOS score 6, range 4–9), and the most common source of bias was short follow-up periods and limited inclusion of potential confounders in final analyses.

Regarding outcomes, hypertension was defined according to objective measurement in 9 studies.^{13–16,23–26,33} Bradycardia and heart rate changes were evaluated according to objective measurement in 17 studies,^{13,15–17,19,22–31,33,34} and one study reported data on bradycardia from a database.³² After a median follow-up of 24 weeks (range 3–463 weeks), AChEI use was associated with a higher proportion of hypertension in 7 studies compared to baseline (1,573 individuals, 4%, 95% CI=2–8%, $p < .001$, $I^2=47%$) and bradycardia in 12 studies (13,703 participants, 2%, 95% CI=1–6%, $p < .001$, $I^2=98%$).

This latter finding was partly confirmed when treating heart rate as a continuous variable in 13 studies including 607 participants in which the use of AChEIs was associated with a nonsignificant decrease in heart rate from baseline (SMD=−1.77, 95% CI=−3.58–0.03, $p=.05$, $I^2=78%$) (Table 1).

Regarding ECG findings, the use of AChEI was associated with a prolongation of the PR interval at follow-up (SMD=0.10, 95% CI=0.008–0.19, $p=.03$, $I^2=3%$), which remained statistically significant after adjustment for publication bias (Table 1).

Sensitivity Analysis

Supplementary Table S4 shows the same analyses reported in Table 1 stratified for possibly relevant cofactors. Heart rate reductions from baseline were seen only in studies conducted in Europe, not in those from Asia and North America (p for interaction=.01). Reductions in heart rate were significant only in those diagnosed with AD, but the interaction was not significant (p for interaction=.09), and only one study reported heart rate as outcome in a non-AD cohort. Finally, use of galantamine was associated with a significant reduction in diastolic blood pressure from baseline to follow-up, contrary to donepezil or rivastigmine (p for interaction=.004). Meta regression suggested that the length of follow-up did not affect any of the results.

Findings of Cohort Studies

Overall, 9 large studies reported CV outcomes or proxies in people taking AChEI and controls.^{35–43} Four of these studies were mainly conducted in community-dwelling older adults, and 7 included of all 3 AChEIs (Supplementary Table S3). A total of 243,499 participants with dementia were compared with 2,246,592 controls, with no significant differences in terms of mean age (78.4 ± 7.3 vs 78.5 ± 8.4 , $p=.89$) or percentage of women (52.1% in both groups, $p > .99$) (Supplementary Table S3). The quality of these studies was good (NOS score median 7, range 6–9).

After adjusting for a median of 4 potential confounders (range 0–12) over 116 weeks of follow-up (range 42–520 weeks), the use of an AChEI was associated with

Table 1. Meta-analysis of Longitudinal Study Findings on Blood Pressure, Clinical, and Electrocardiographic Parameters

Parameter	Studies	Participants n	Meta-Analysis			Publication Bias			Classic Fail Safe, N
			Effect Size (95% CI)	P-Value	I ² , % (Heterogeneity)	Egger Bias	P-Value	Trim and Fill (95% CI) [Trimmed]	
Hypertension	7	1,573	4 (2–8)/100 ^a	<.001	47	2.88	.32	Unchanged	691
Systolic blood pressure	11	610	−0.04 (−0.13–0.04) ^b	.31	8	0.80	.49	Unchanged	0
Diastolic blood pressure	11	610	0.00 (−0.26–0.27) ^b	.97	95	2.90	.05	0.24 (−0.13–0.62) [5]	202
Bradycardia	12	13,703	2 (1–6) ^a	<.001	98	−2.49	.47	3 (0–7) [2]	4,896
Heart rate	13	607	−1.77 (−3.58–0.03) ^b	.05	78	0.81	.19	−1.08 (−2.73–0.59) [4]	1,747
PR interval	14	517	0.10 (0.008–0.19) ^b	.03	3	−2.00	.05	0.18 (0.08–0.28) [5]	0
QRS interval	10	517	0.03 (−0.06–0.12) ^b	.50	0	−0.47	.31	0.04 (−0.04–0.12) [2]	0
QTc interval	15	1,622	−0.04 (−0.11–0.04) ^b	.34	42	0.87	.32	−0.11 (−0.20 to −0.04) [6]	0

^a(Events/baseline population)*100.

^bStandardized mean differences (calculated change from baseline to follow-up).

CI = confidence interval.

significantly lower risk of CV events (stroke, acute myocardial infarction, acute coronary syndrome, CV mortality) (HR=0.63, 95% CI=0.45–0.88, $p=.008$, $I^2=18\%$) (Figure 1). Publication bias did not affect these findings.

In Figure 2, we report the association between AChEI use and bradycardic events (bradycardia in 3 studies, onset of atrioventricular block with consequent hospitalization in 1 study). AChEI use was not associated with risk of any bradycardic event in these studies (HR=1.40, 95% CI=0.76–2.59, $p=.28$), but these results had high heterogeneity ($I^2=98\%$). No publication bias was evident. In a sensitivity analysis, after excluding the only study reporting a protective effect of AChEIs against bradycardic events (the study with the largest sample size),³⁷ we observed an increased risk of bradycardia (HR=1.59, 95% CI=1.32–1.92, $p<.001$), with a concomitant reduction in heterogeneity ($I^2=35\%$).

DISCUSSION

This meta-analysis of 22 longitudinal studies found that AChEI therapy was associated with greater risk of bradycardia and hypertension. The use of AChEIs was

associated with PR interval prolongation and although not a significant reduction in heart rate. In 9 cohort studies comparing participants taking AChEIs with controls, use of AChEIs was associated with a 37% lower risk of CV events, whereas the evidence regarding bradycardic events was equivocal.

AChEIs have demonstrated efficacy for stabilizing memory decline and delaying functional disability in individuals with dementia by increasing cholinergic transmission in the brain,¹ but this increase in cholinergic activity can affect cardiac function and may cause adverse effects such as negative chronotropic events, arrhythmia, and hypotension.⁴⁴ Older adults treated with AChEIs may be prone to these adverse events because of the high prevalence of cardiac and vascular comorbidities; co-prescription of antihypertensives, antiarrhythmics, antipsychotics, and antidepressants; and aging-associated changes in the cardiac conduction system.⁴⁴ AChEIs are generally known to be safe for the cardiac conduction system, but a limited number of case reports indicate development of atrioventricular block with AChEI therapy.⁴⁴

This meta-analysis suggests that individuals with dementia treated with AChEIs were at greater risk of

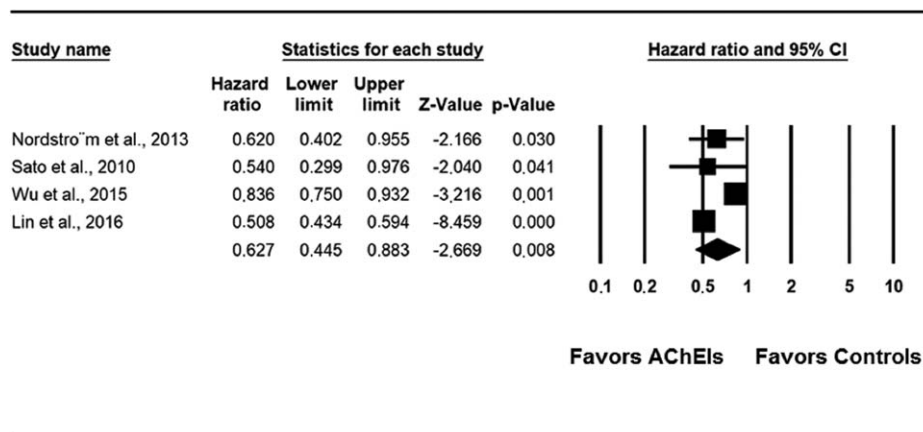


Figure 1. Comparison of cardiovascular events in individuals taking acetylcholinesterase inhibitors and controls.

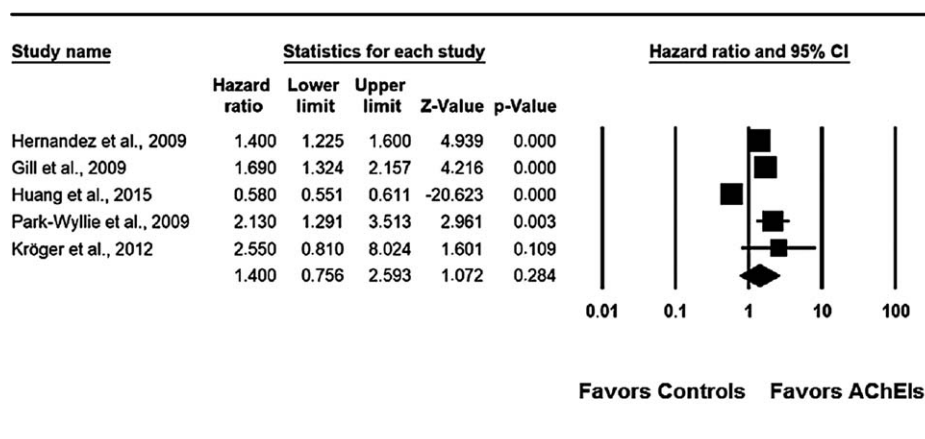


Figure 2. Comparison of bradycardic events in individuals taking acetylcholinesterase inhibitors and controls.

bradycardia, but that this heart rate reduction was not significantly associated with hospitalization due to bradycardia-induced events. The decrease in heart rate was more pronounced in studies conducted in Europe, which might be explained through the larger number of studies in this region and possible preponderance of participants prone to autonomic changes. The effect of AChEIs in lowering heart rate was only partly confirmed in cohort studies because the use of these drugs was associated with greater risk of bradycardic events only after excluding an outlier study.³⁷

This study³⁷ included the largest number of individuals with dementia, 7 times as many as the other studies, and accounted for a substantial portion of the participants included in our meta-analysis. Moreover, this study used no covariates to adjust in its analysis, adding another important potential bias. We believe that this study may have introduced an important bias to our findings because, after it was removed in the sensitivity analyses, AChEIs were found to increase the risk of bradycardic events by 59%. It is likely that, as the authors of that study stated, anecdotal cases of bradycardia in individuals taking AChEIs have led to greater awareness of the possible development of bradycardia, resulting in a more cautious approach to drug prescribing and symptom management.³⁷

Another remarkable clinical finding of this meta-analysis is the association between AChEI therapy and an approximately 37% lower risk of CV events. Several mechanisms could explain this relationship. First, similar to parasympathetic activity through vagal stimulation or exercise, AChEIs might have a protective role against heart failure and CV diseases. A number of previous studies found that parasympathetic activity has direct positive effects at the ventricular level independent of its sinus node effects.⁴ Greater cholinergic activity has also benefits by affecting CV events through other potential mechanisms, including antiinflammatory pathways, modulation of nitric oxide signaling, regulation of redox states, improvement in mitochondrial biogenesis and function, and potential calcium regulation.⁴ AChEIs might also protect cardiomyocytes against acute hypoxia and ischemia

by increasing cholinergic activity in the heart.⁴⁵ Second, it was reported that cholinesterase inhibition reduced levels of thrombomodulin, a marker of endothelial activation, and β -thromboglobulin, a marker of platelet activation. Thus, AChEIs might prevent vascular endothelial damage and play a cytoprotective role in endothelial function.⁴⁶ Third, an adverse CV risk factor profile is associated with poorer cognitive function, and inversely, the direct positive effects of AChEIs on cognitive function might also influence the lower overall risk of death.⁴⁷ Last, AChEIs therapy contributes to weight loss in patients with dementia, with a 2-fold risk, which might indirectly influence CV risk,⁴⁸ although in some instances, people with dementia may not be able to notify health providers of health changes, or staff may not recognize changes. Thus, this is a potential limitation of these studies.

Finally, in sensitivity analyses of longitudinal studies, we found that use of galantamine, but not donepezil or rivastigmine, was associated with a significant reduction in diastolic blood pressure from baseline, which might be related to the allosterically modulating effect of galantamine on the nicotinic and muscarinic acetylcholine receptors to potentiate the sensitivity to acetylcholine in addition to AChEI inhibiting properties.⁴⁹ Furthermore, we found that, although individuals treated with AChEIs had a significant prolongation in PR interval, no significant changes in the QRS or QT/QTc intervals, which can lead to electrical instability and risk of ventricular arrhythmogenesis, were detected.

Although many studies and participants were included, and we found no evidence of publication bias in our meta-analysis, there are some limitations that should be mentioned. No randomized controlled trials were included. Although AChEIs are well established in clinical practice, concerns about their cardiac safety remain. Initial data on safety came from randomized controlled trials conducted in subjects with good CV health.^{50,51} In recent years, a number of open-label and observational studies examining cohorts more similar to real-world clinical populations have been published. Hence, the aim of our study was to examine CV outcomes in these forms of studies. Another limitation is that the effects of AChEIs on

different types of dementia were not evaluated because of the limited number of participants with non-AD dementias. In addition, only a few studies contained data on disability, which might be indicator of physical health, although in some instances, people with dementia may not be able to notify health providers of health changes, or staff may not recognize changes. Thus, this is a potential limitation of these studies. Lastly, most of the studies did not evaluate co-prescriptions (e.g., antihypertensives, anti-arrhythmics, antipsychotics, antidepressants) that may affect the CV system and did not have a true control group. Thus, we were not able to assess whether these medications influenced our results.

In conclusion, the use of AChEIs was associated with a significant 37% reduction in CV events, including stroke, acute myocardial infarction, and acute coronary syndrome. Although AChEI therapy appears to be associated with risk of bradycardia, the association with severe bradycardic events needs further evaluation. In light of our findings, AChEIs appear to be safe in older adults with dementia, but when prescribing AChEIs, particular care should be taken in those with preexisting bradycardia or taking heart rate-limiting medications. Further studies are required to compare the relative risk and benefit of different AChEIs, taking into consideration CV outcomes (e.g., analyses in individuals with preexisting heart disease).

ACKNOWLEDGMENTS

Brendon Stubbs is partially funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley National Health Service (NHS) Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health. BS is supported by the Health Education England and the National Institute for Health Research HEE/NIHR ICA Programme Clinical Lectureship (ICA-CL-2017-03-001).

Conflict of Interest: None.

Author Contributions: Isik, Mueller, Veronese, Stubbs, Soysal: study design, data analysis, manuscript writing. Soysal, Stubbs: data collection. Veronese: statistical and data analysis. Solmi, Basso, Maggi, Schofield, Mueller: manuscript writing.

Sponsor's Role: None.

REFERENCES

- Isik AT. Late onset Alzheimer's disease in older people. *Clin Interv Aging* 2010;5:307–311.
- Masuda Y. Cardiac effect of cholinesterase inhibitors used in Alzheimer's disease—from basic research to bedside. *Curr Alzheimer Res* 2004;1:315–321.
- Malone DM, Lindsay J. Cholinesterase inhibitors and cardiovascular disease: A survey of old age psychiatrists' practice. *Age Ageing* 2007;36:331–333.
- He X, Zhao M, Bi X, et al. Novel strategies and underlying protective mechanisms of modulation of vagal activity in cardiovascular diseases. *Br J Pharmacol* 2015;172:5489–5500.
- Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *PLoS Med* 2009;6:e1000100.
- Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analyses (online). Available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp Accessed February 25, 2018.
- Gill SS, Bronskill SE, Mamdani M, et al. Representation of patients with dementia in clinical trials of donepezil. *Can J Clin Pharmacol* 2004;11:e274–285.
- Buffel du Vaure C, Dechartres A, Battin C, et al. Exclusion of patients with concomitant chronic conditions in ongoing randomised controlled trials targeting 10 common chronic conditions and registered at ClinicalTrials.gov: A systematic review of registration details. *BMJ Open* 2016;6:e012265.
- Luchini C, Stubbs B, Solmi M, et al. Assessing the quality of studies in meta-analyses: Advantages and limitations of the Newcastle Ottawa Scale. *World J Metaanal* 2017;5:80–84.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–1558.
- Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088–1101.
- Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–634.
- Isik AT, Soysal P, Yay A. Which rivastigmine formula is better for heart in elderly patients with Alzheimer's disease: Oral or patch? *Am J Alzheimers Dis Other Demen* 2014;29:735–738.
- Bär K-J, Boettger MK, Seidler N, et al. Influence of galantamine on vasomotor reactivity in Alzheimer's disease and vascular dementia due to cerebral microangiopathy. *Stroke* 2007;38:3186–3192.
- van Beek AH, Sijbesma JC, Olde Rikkert MG, et al. Galantamine does not cause aggravated orthostatic hypotension in people with Alzheimer's disease. *J Am Geriatr Soc* 2010;58:409–410.
- Bordier P, Garrigue S, Lanusse S, et al. Cardiovascular effects and risk of syncope related to donepezil in patients with Alzheimer's disease. *CNS Drugs* 2006;20:411–417.
- Doody RS, Corey-Bloom J, Zhang R, et al. Safety and tolerability of donepezil at doses up to 20 mg/day: Results from a pilot study in patients with Alzheimer's disease. *Drugs Aging* 2008;25:163–174.
- Doody RS, Geldmacher DS, Farlow MR, et al. Efficacy and safety of donepezil 23 mg versus donepezil 10 mg for moderate-to-severe Alzheimer's disease: A subgroup analysis in patients already taking or not taking concomitant memantine. *Dement Geriatr Cogn Disord* 2012;33:164–173.
- Farlow M, Veloso F, Moline M, et al. Safety and tolerability of donepezil 23 mg in moderate to severe Alzheimer's disease. *BMC Neurol* 2011;11:57.
- Figiel GS, Sadowsky CH, Strigas J, et al. Safety and efficacy of rivastigmine in patients with Alzheimer's disease not responding adequately to donepezil: an open-label study. *Prim Care Companion J Clin Psychiatry* 2008;10:291–298.
- Figiel GS, Koumaras B, Meng X, et al. Long-term safety and tolerability of rivastigmine in patients with Alzheimer's disease switched from donepezil: An open-label extension study. *Prim Care Companion J Clin Psychiatry* 2008;10:363–367.
- Igeta H, Suzuki Y, Tajiri M, et al. Cardiovascular pharmacodynamics of donepezil hydrochloride on the PR and QT intervals in patients with dementia. *Hum Psychopharmacol* 2014;29:292–294.
- Isik AT, Yildiz GB, Bozoglu E, et al. Cardiac safety of donepezil in elderly patients with Alzheimer disease. *Intern Med* 2012;51:575–578.
- Isik AT, Bozoglu E, Naharci MI, et al. Evaluation of the effects of galantamine on cardiac function in elderly patients with Alzheimer's disease. *Am J Geriatr Pharmacother* 2010;8:454–459.
- Isik AT, Bozoglu E, Yay A, et al. Which cholinesterase inhibitor is the safest for the heart in elderly patients with Alzheimer's disease? *Am J Alzheimers Dis Other Demen* 2012;27:171–174.
- Kubo T, Sato T, Noguchi T, et al. Influences of donepezil on cardiovascular system—possible therapeutic benefits for heart failure—Donepezil Cardiac Test Registry (DOCTER) study. *J Cardiovasc Pharmacol* 2012;60:310–314.
- McLaren AT, Allen J, Murray A, et al. Cardiovascular effects of donepezil in patients with dementia. *Dement Geriatr Cogn Disord* 2003;15:183–188.
- Van Puyvelde K, Mets T. Galantamine (Reminyl) once daily outcome and satisfaction survey (RODOS) in mild to moderate Alzheimer's disease: A study in a real life population. *Geriatr Gerontol Int* 2011;11:256–261.
- Riepe MW. High-dose cholinergic therapy with rivastigmine patch does not prolong QTc time in patients with Alzheimer's disease. *J Clin Psychiatry* 2014;75:288.
- Sadowsky CH, Dengiz A, Olin JT, et al. Switching from donepezil tablets to rivastigmine transdermal patch in Alzheimer's disease. *Am J Alzheimers Dis Other Demen* 2009;24:267–275.

31. Sobow T, Kloszewska I. Cholinesterase inhibitors in the “real world” setting: Rivastigmine versus donepezil tolerability and effectiveness study. *Arch Med Sci* 2006;2:194–198.
32. Ali TB, Schleret TR, Reilly BM, et al. Adverse effects of cholinesterase inhibitors in dementia, according to the pharmacovigilance databases of the United-States and Canada. *PLoS One* 2015;10:e0144337.
33. Masuda Y, Kawamura A. Acetylcholinesterase inhibitor (donepezil hydrochloride) reduces heart rate variability. *J Cardiovasc Pharmacol* 2003;41 Suppl 1:S67–S71.
34. Zhang Z, Yu L, Gaudig M, et al. Galantamine versus donepezil in Chinese patients with Alzheimer’s disease: Results from a randomized, double-blind study. *Neuropsychiatr Dis Treat* 2012;8:571–577.
35. Gill SS, Anderson GM, Fischer HD, et al. Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors: A population-based cohort study. *Arch Intern Med* 2009;169:867–873.
36. Hernandez RK, Farwell W, Cantor MD, et al. Cholinesterase inhibitors and incidence of bradycardia in patients with dementia in the Veterans Affairs New England healthcare system. *J Am Geriatr Soc* 2009;57:1997–2003.
37. Huang AR, Redpath CJ, van Walraven C. The influence of cholinesterase inhibitor therapy for dementia on risk of cardiac pacemaker insertion: A retrospective, population-based, health administrative databases study in Ontario, Canada. *BMC Neurol* 2015;15:66.
38. Kroger E, Berkers M, Carmichael PH, et al. Use of rivastigmine or galantamine and risk of adverse cardiac events: A database study from the Netherlands. *Am J Geriatr Pharmacother* 2012;10:373–380.
39. Lin YT, Wu PH, Chen CS, et al. Association between acetylcholinesterase inhibitors and risk of stroke in patients with dementia. *Sci Rep* 2016;6:29266.
40. Nordstrom P, Religa D, Wimo A, et al. The use of cholinesterase inhibitors and the risk of myocardial infarction and death: A nationwide cohort study in subjects with Alzheimer’s disease. *Eur Heart J* 2013;34:2585–2591.
41. Park-Wyllie LY, Mamdani MM, Li P, et al. Cholinesterase inhibitors and hospitalization for bradycardia: A population-based study. *PLoS Med* 2009;6:e1000157.
42. Sato K, Urbano R, Yu C, et al. The effect of donepezil treatment on cardiovascular mortality. *Clin Pharmacol Ther* 2010;88:335–338.
43. Wu PH, Lin YT, Hsu PC, et al. Impact of acetylcholinesterase inhibitors on the occurrence of acute coronary syndrome in patients with dementia. *Sci Rep* 2015;5:15451.
44. Soysal P, Isik AT. Asymptomatic bradycardia due to rivastigmine in an elderly adult with Lewy body dementia. *J Am Geriatr Soc* 2015;63:2648–2650.
45. Kakinuma Y, Ando M, Kuwabara M, et al. Acetylcholine from vagal stimulation protects cardiomyocytes against ischemia and hypoxia involving additive non-hypoxic induction of HIF-1alpha. *FEBS Lett* 2005;579:2111–2118.
46. Borroni B, Agosti C, Martini G, et al. Cholinesterase inhibitors exert a protective effect on endothelial damage in Alzheimer disease patients. *J Neurol Sci* 2005;229–230:211–213.
47. Mueller C, Perera G, Hayes RD, et al. Associations of acetylcholinesterase inhibitor treatment with reduced mortality in Alzheimer’s disease: A retrospective survival analysis. *Age Ageing* 2018;47:88–94.
48. Soysal P, Isik AT, Stubbs B, et al. Acetylcholinesterase inhibitors are associated with weight loss in older people with dementia: A systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2016;87:1368–1374.
49. Tsvetkova D, Obreshkova D, Zheleva-Dimitrova D, et al. Antioxidant activity of galantamine and some of its derivatives. *Curr Med Chem* 2013;20:4595–4608.
50. Ballard C, Sauter M, Scheltens P, et al. Efficacy, safety and tolerability of rivastigmine capsules in patients with probable vascular dementia: The VantagE study. *Curr Med Res Opin* 2008;24:2561–2574.
51. Farlow MR, Salloway S, Tariot PN, et al. Effectiveness and tolerability of high-dose (23 mg/d) versus standard-dose (10 mg/d) donepezil in moderate to severe Alzheimer’s disease: A 24-week, randomized, double-blind study. *Clin Ther* 2010;32:1234–1251.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Table S1. Search Strategy—Example for PubMed Search

Table S2. Descriptive characteristics of the longitudinal studies included.

Table S3. Descriptive characteristics of cohort studies

Table S4. Strata for mean differences for blood pressure and electrocardiographic parameters in people taking acetylcholinesterase inhibitors.

Figure S1. PRISMA flow chart.

Please note: Wiley-Blackwell is not responsible for the content, accuracy, errors, or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.