Risk of Bradycardia and Syncope Associated with the Use of Cholinesterase Inhibitors in Patients with Alzheimer's Disease and Related Dementias: A Systematic Review and Meta-Analysis

Chijioke Okeke, Tenia Slade, Sarah Beth Tucker, Olivia Whitworth, Amey Rane, Bryan Love, Ibraheem Karaye, Saud Alsahali, Nasim Maleki, Nawaf Alotaibi, Douglas Thornton, Ismaeel Yunusa

Submitted to: JMIR Aging
on: February 12, 2025

Table of Contents

Original Manuscript **5**
Supplementary Files **38**
Multimedia Appendixes **39**
Multimedia Appendix 1 ..... **39**

Risk of Bradycardia and Syncope Associated with the Use of Cholinesterase Inhibitors in Patients with Alzheimer's Disease and Related Dementias: A Systematic Review and Meta-Analysis

Chijioke Okeke[1] PharmD; Tenia Slade[2] PharmD; Sarah Beth Tucker[2] BM; Olivia Whitworth[2] PharmD; Amey Rane[3] PhD; Bryan Love[2] PharmD; Ibraheem Karaye[4] MD, DrPH; Saud Alsahali[5] PhD; Nasim Maleki[6] PhD; Nawaf Alotaibi[4] PhD; Douglas Thornton[1] PhD; Ismaeel Yunusa[2] PharmD, PhD

[1]Prescription Misuse Education and Research (PREMIER) Center College of Pharmacy University of Houston System Houston US
[2] College of Pharmacy University of South Carolina Columbia US
[3] MCPHS University Boston US
[4] Department of Population Health Hofstra University Hempstead US
[5]Department of Pharmacy Practice College of Pharmacy Qassim University Qassim SA
[6]Department of Psychiatry Massachusetts General Hospital, Harvard Medical Schoo Harvard University Cambridge US

Corresponding Author:
Ismaeel Yunusa PharmD, PhD

College of Pharmacy
University of South Carolina
715 Sumter Street
Columbia
US

Abstract

Background: In some cases, cholinesterase inhibitors (ChEIs) can amplify the effect of acetylcholine on vagal stimulation of the heart, which may lead to syncope and bradycardia. Available evidence does not definitively establish this association, and therefore clinicians may be unaware of it.

Objective: To systematically review and perform a meta-analysis of the risk of bradycardia and syncope in patients with Alzheimer's Disease and Related Dementias (ADRD) treated with ChEIs.

Methods: Our data sources were PubMed, EMBASE, Cochrane Library, and reference lists of relevant articles. Databases were searched from inception to June 15, 2024. We included randomized controlled trials and observational studies (cohort and case-control studies). Three reviewers independently extracted data per PRISMA recommendations and assessed the quality of each study with the National Heart, Lung, and Blood Institute quality assessment tools. We used random-effects modeling to estimate pooled relative risks (RRs) and their 95% confidence intervals (CIs). The outcomes examined were bradycardia and syncope.

Results: Twenty-five independent studies (sixteen RCTs, seven cohorts, one case-control, one pragmatic trial; n=258,388) were included in the systematic review and meta-analysis out of the original 310 studies identified. The median reported age in the studies included was 76.3 years (range from 70 to 89.2). In most studies (18 out of 25), more than half of the individuals were female. Additionally, 18 (72%) of the studies included patients with Alzheimer’s disease. The overall absolute risk of bradycardia was 4.63% (95% CI, 1.80-8.55%; 16 studies, n=97,165), and that of syncope was 2.31% (95% CI, 1.18-3.77%; 16 studies, n= 134,162). Use of ChEIs in patients with ADRD was significantly associated with increased risk of bradycardia (RR: 1.23 [95% CI: 1.14-1.33]; 6 studies, n=97,396) and syncope (RR: 1.40 [95% CI: 1.20-1.64]; 9 studies, n=85,169) compared to non-use.

Conclusions: This systematic review and meta-analysis suggest that patients with ADRD treated with ChEIs have an increased risk of bradycardia and syncope. Therefore, clinicians should consider the risk of bradycardia and syncope against the benefits of ChEIs when treating patients with ADRD.

(JMIR Preprints 12/02/2025:72510)
DOI: https://doi.org/10.2196/preprints.72510

Preprint Settings

1) Would you like to publish your submitted manuscript as preprint?

✓ **Please make my preprint PDF available to anyone at any time (recommended).**
Please make my preprint PDF available only to logged-in users; I understand that my title and abstract will remain visible to all users.
Only make the preprint title and abstract visible.
No, I do not wish to publish my submitted manuscript as a preprint.

2) If accepted for publication in a JMIR journal, would you like the PDF to be visible to the public?

✓ **Yes, please make my accepted manuscript PDF available to anyone at any time (Recommended).**
Yes, but please make my accepted manuscript PDF available only to logged-in users; I understand that the title and abstract will remain v
Yes, but only make the title and abstract visible (see Important note, above). I understand that if I later pay to participate in <a href="http
No. Please do not make my accepted manuscript PDF available to anyone.

Original Manuscript

Risk of Bradycardia and Syncope Associated with the Use of Cholinesterase Inhibitors in Patients with Alzheimer's Disease and Related Dementias: A Systematic Review and Meta-Analysis

Authors:

Chijioke M. Okeke, BPharm[1], Tenia Slade, PharmD[2]; Sarah Beth Tucker, BM[2]; Olivia Whitworth, PharmD[2]; Amey Rane, MS, PhD[3]; Bryan Love, PharmD, MPH[2]; Ibraheem M. Karaye, MD, DrPH[4]; Saud Alsahali, PhD[5]; Nasim Maleki, PhD[6]; Nawaf M Alotaibi, PhD[4]; Douglas Thornton, PharmD, PhD[1]; Ismaeel Yunusa, PharmD, PhD[2]

Affiliations:

[1] Prescription Misuse Education and Research (PREMIER) Center, University of Houston College of Pharmacy, Houston, TX
[2]University of South Carolina College of Pharmacy, Columbia, SC
[3] Massachusetts College of Pharmacy and Health Sciences, Boston, MA
[4] Department of Population Health, Hofstra University, Hempstead, NY
[5]Department of Pharmacy Practice, College of Pharmacy, Qassim University, Buraidah, Qassim, Saudi Arabia
[6]Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA
[7]Department of Clinical Pharmacy, College of Pharmacy, Northern Border University, Rafha, Saudi Arabia

Correspondence:

Ismaeel Yunusa, PharmD, PhD
Department of Clinical Pharmacy and Outcomes Sciences,
University of South Carolina College of Pharmacy,
715 Sumter Street, Columbia, SC 29208
Email: iyunusa@mailbox.sc.edu
Phone: 803-777-7888

Word Count: *Manuscript: 2447, Abstract: 339*

ABSTRACT

Background/Importance: In some cases, cholinesterase inhibitors (ChEIs) can amplify the effect of acetylcholine on vagal stimulation of the heart, which may lead to syncope and bradycardia. Available evidence does not definitively establish this association, and therefore clinicians may be unaware of it.

Objective: To systematically review and perform a meta-analysis of the risk of bradycardia and syncope in patients with Alzheimer's Disease and Related Dementias (ADRD) treated with ChEIs.

Methods: Our data sources were PubMed, EMBASE, Cochrane Library, and reference lists of relevant articles. Databases were searched from inception to June 15, 2024. We included randomized controlled trials and observational studies (cohort and case-control studies). Three reviewers independently extracted data per PRISMA recommendations and assessed the quality of each study with the National Heart, Lung, and Blood Institute quality assessment tools. We used random-effects modeling to estimate pooled relative risks (RRs) and their 95% confidence intervals (CIs). The outcomes examined were bradycardia and syncope.

Results: Twenty-five independent studies (sixteen RCTs, seven cohorts, one case-control, one pragmatic trial; n=258,388) were included in the systematic review and meta-analysis out of the original 310 studies identified. The median reported age in the studies included was 76.3 years (range from 70 to 89.2). In most studies (18 out of 25), more than half of the individuals were female. Additionally, 18 (72%) of the studies included patients with Alzheimer’s disease. The overall absolute risk of bradycardia was 4.63% (95% CI, 1.80-8.55%; 16 studies, n=97,165), and

that of syncope was 2.31% (95% CI, 1.18-3.77%; 16 studies, n= 134,162). Use of ChEIs in patients with ADRD was significantly associated with increased risk of bradycardia (RR: 1.23 [95% CI: 1.14-1.33]; 6 studies, n=97,396) and syncope (RR: 1.40 [95% CI: 1.20-1.64]; 9 studies, n=85,169) compared to non-use.

Conclusions and Relevance: This systematic review and meta-analysis suggest that patients with ADRD treated with ChEIs have an increased risk of bradycardia and syncope. Therefore, clinicians should consider the risk of bradycardia and syncope against the benefits of ChEIs when treating patients with ADRD.

INTRODUCTION

For most of the 50 million individuals worldwide with Alzheimer's disease and related dementias (ADRD), cholinesterase inhibitors (ChEIs) are a mainstay of treatment to improve symptoms of memory loss and potentially forestall behavioral and functional declines.[1,2] However, in some cases, ChEIs can amplify the effect of acetylcholine on vagal stimulation of the heart, which may lead to syncope, bradycardia,[3,4] and subsequent inappropriate prescribing cascade.[5,6] Available evidence does not definitively establish the association; however, and therefore clinicians may be unaware of it. Without awareness of this possible causal relationship, clinicians might even consider permanent pacemaker insertion[5,7] in patients receiving ChEIs. To avoid downstream cascading events such as these,[8] it is imperative to first closely examine and synthesize current evidence of this association and then, if warranted, improve clinician awareness and vigilance.

Randomized clinical trials (RCTs) did not suggest a causal relationship between ChEI use and bradycardia and syncope because they are primarily statistically powered to establish efficacy and lack sufficient statistical power to assess safety outcomes,[9–12] Some observational studies suggested an association while others did not[5,13–16]. Two systematic reviews and meta-analyses of adverse health outcomes associated with ChEI use indicated that ChEIs use might result in bradycardia and syncope.[17,18] However, these studies did not perform a focused and comprehensive assessment of evidence for this relationship. Moreover, since the publication of these meta-analyses, additional studies providing data on bradycardia and syncope following the use of ChEIs have been published[5,15,19,20]. Therefore, this systematic review and meta-analysis aimed to examine the association of ChEI use with the risk of bradycardia and syncope.

METHODS

Study Protocol

The protocol for this study was a priori registered with PROSPERO International Prospective Register of Systematic Reviews (CRD42022308730).[21] In addition, the study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 reporting guideline statement.[22] Ethical review and informed consent were waived because the study used secondary data from previous studies**.**

Data Sources and Searches

We methodically searched PubMed, EMBASE, and Cochrane Library from inception to June 15, 2024. The search criteria included MeSH terms (for PubMed and Cochrane), Emtree terms (for EMBASE) and text words for '*dementia'* along with terms for '*cholinesterase inhibitors'*, '*bradycardia'*, and '*syncope'* (See **Supplement**). The search was supplemented by conducting a secondary search on the reference lists of initially identified studies obtained from the primary search to find additional relevant articles. We also manually searched for gray literature on clinical trial registries.

Study Selection

Two reviewers independently searched for RCTs and observational studies of ChEI medications (donepezil, rivastigmine, or galantamine) that also reported syncope (defined as a temporary loss of consciousness resulting from a fall in blood pressure),[23] or bradycardia (defined as heartbeats fewer than 60 times per minute),[24] according to predefined inclusion and exclusion criteria. Studies were eligible when (1) they included persons with ADRD (2) receiving treatment with a ChEI vs. placebo, a different ChEI, memantine or other drugs (3) reported outcomes of bradycardia and syncope (4) an RCT or observational study (cohort and/or case-control study).

Studies of patients with ADRD treated with ChEIs were excluded when (1) they did not report outcomes of bradycardia and syncope (2) not RCT or observational study. Eligible studies were identified and independently selected by 2 reviewers who screened titles, abstracts, and citations and evaluated full-text records using Rayyan-QCRI software (Rayyan).[25] We resolved disagreements in selecting eligible studies through discussions with the research team members until a consensus was reached.

Data Extraction and Quality Assessments

At least two reviewers independently extracted data using a standardized predefined data extraction form in Microsoft Excel. Extracted data included the last name of the first author, publication year, study design, patient mean/median age, patient sex, type of ChEI, comparator, number of persons in each study arm, number of individuals with either bradycardia or syncope per study arm, study follow-up duration, study quality, type of dementia, and level of cognition at baseline (including Mini-Mental State Exam [MMSE] at baseline).

The quality of each included study was assessed independently by three reviewers using the National Heart, Lung, and Blood Institute quality assessment tools.[26] In addition, we resolved discrepancies in data extraction and study quality assessments through a discussion with the study team members to reach a consensus.

Data Synthesis

We estimated the pooled absolute risks of the outcomes by conducting a random-effects meta-analysis of the cumulative incidence (incidence proportions or absolute risk) of bradycardia and syncope in persons exposed to ChEIs. The random-effects model was chosen to account for variations both within and between studies, providing a more generalized inference of the potential effects of ChEIs across different populations and study conditions. Additionally, we estimated the pooled relative risks (RRs) of the outcomes compared to non-use of ChEIs, along with their 95% confidence intervals (CIs), using random-effects models based on the restricted maximum likelihood (REML) method.[27] The REML method was selected because it is known for being less biased and more efficient than many other methods, providing reliable estimates.[27]

Additional and Sensitivity Analyses

We evaluated heterogeneity using the I^2 statistic and Cochrane's Q tests to quantify the variability across studies. The I^2 index provides an estimate of the percentage of variability in results across studies that is due to real differences rather than chance, with values less than 25% indicating low heterogeneity, 25%-50% indicating moderate heterogeneity, and over 50% indicating high heterogeneity.[28] Cochrane's Q test, based on a chi-square distribution, tests the null hypothesis that the true treatment effect is the same across all studies, with a significant result suggesting larger variation across studies rather than within individual studies.[28]

To assess publication bias, we visually inspected funnel plots, conducted Egger's and Begg's tests, as well as trim and fill adjustment.[29] These analyses were performed for pooled estimates of absolute risks for both study outcomes. They were not conducted for pooled RR estimates, as

these tests have limited statistical power to distinguish funnel plot asymmetry from chance findings when the number of studies is fewer than ten. [30]Sensitivity analyses were performed to affirm the robustness and reliability of the findings. These analyses were based on a leave-one-out approach, where each study was sequentially excluded to determine its influence on the overall pooled estimates.[31]

RESULTS

Search Results

After removing duplicates and other ineligible studies as marked by automation tools, we retrieved 221 unique citations**,** 25 of which were selected for inclusion in the systematic review. We excluded some studies during abstract or full-text screening for reasons that include the wrong population, intervention, or study designs. Studies written in non-English languages or lacking abstracts were also excluded. (*Figure 1*).

Characteristics of Included Studies

Twenty-five independent studies (sixteen RCTs, seven cohorts, one case-control, one pragmatic trial; n=258,388) were included in the systematic review and meta-analysis out of the original 221 studies identified *(Table 1)*[8,15,32–54]. Nine of the studies were conducted purely in the United States[15,34,39,41–43,48,50,52], while the rest were conducted in European countries or in multiple locations, including the US and Canada. The median reported age in the studies included was 76.3 years (range from 70 to 89.2). In most studies (18 out of 25), more than half of the individuals were female. A majority of the experimental studies compared ChEIs (donepezil, rivastigmine, galantamine, etc.) to placebo.[32,33,35,41,43,47,48,51,53,54] Some RCTs, however, compared

ChEI therapy to other ChEIs.[34,39,40,42,45,49,50] One retrospective cohort study compared the outcomes of ChEI interventions to memantine monotherapy or a combination of ChEI and memantine.[52]

Risk of Bradycardia and Syncope

The pooled analysis of 16 studies (n=97,165) estimated the absolute risk of bradycardia to be 4.63% (95% CI, 1.80-8.55%) *(Fig 2A).* Patients treated with ChEIs had a significantly higher risk of bradycardia compared to those not receiving ChEIs (RR, 1.23; 95% CI, 1.14-1.33; 6 studies; n=97,396) *(Fig 2B).*

Similarly, the pooled analysis of 16 studies (n=134,162) showed an absolute risk of syncope of 2.31% (95% CI, 1.18-3.77%) *(Fig 3A).* After adjusting for publication bias using the trim and fill method, the estimated risk increased to 9.92% (95% CI, 5.12-16.03). ChEI use was associated with a significantly increased risk of syncope compared to nonuse (RR: 1.40; 95% CI, 1.20-1.64; 9 studies, n=85,169) *(Fig 3B).*

Sensitivity and Additional Analyses

Sensitivity analyses for bradycardia indicated that none of the individual studies significantly influenced the estimated relative risk (RR). Most point estimates were similar to the primary analysis, and all suggested a significantly increased risk. In contrast, for syncope, one study[5] however, the point estimates remained indicative of an increased risk *(Fig 4A and 4B).*

Regarding publication bias, both Egger's test (p-value = 0.4423) and Begg’s test (p-value = 0.1513) did not suggest significant evidence of publication bias for bradycardia. For syncope, Egger's test did not reveal significant publication bias (p-value = 0.2302), whereas Begg’s test indicated possible publication bias (p-value = 0.0034). *(Supplement)*

Table 1: Characteristics of included studies

Author	Country of Study	Sample Size	Mean age/Median (SD/IQR)	% Female	Study Design	Treatment	Comparator	Follow-up Period	Dementia Type[1]	MMSE at Baseline (SD)	Study Quality
Barone, 2008	European countries	342	72.7 (6.6)	34.8%	RCT	Rivastigmine	Placebo	24 weeks	PD	Elevated homocysteine: 19.2 (3.9) Normal/low homocysteine: 19.6 (3.9)	Good
Black, 2003	US, UK, Canada	603	73.9 (0.3)	44.8%	RCT	Donepezil (5 and 10 mg)	Placebo	24 weeks	VaD	n/a	Good

[11] Abbreviations: VaD: Vascular dementia, AD: Alzheimer's disease, LBW: Lewy body dementia, PD: Parkinson's disease, MCI: Mild cognitive impairment
[2] ChEI(s): Cholinesterase Inhibitors

Author	Country of Study	Sample Size	Mean age/Median (SD/IQR)	% Female	Study Design	Treatment	Comparator	Follow-up Period	Dementia Type	MMSE at Baseline (SD)	Study Quality
Bordier, 2006	France	30	80 (6)	83.3%	Pragmatic Trial	Donepezil 5mg/d x1 month then 10mg/d x7 months	Drug combinations with Donepezil (including β-adrenoceptor antagonists, , amiodarone, flecainide or propafenone).	35 weeks	AD	n/a	Fair
Burns, 2007	US, UK, Canada	579	71.2 (51-91)	55.4%	RCT	Donepezil 5 mg then 10 mg	Placebo	162 weeks	AD	20.1 (0.17)	Good
Burns, 2009	10 European countries	407	84 (6)	80.8%	RCT	Galantamine	Placebo	26 weeks	AD	Galantamine: 8.8 (2.4) Placebo: 9.1 (2.4)	Good
Campbell, 2017	US	196	80.2 (8.4)	74.0%	RCT	Donepezil, Galantamine, or Rivastigmine	other ChEIs[2] in the study	18 weeks	AD	n/a	Poor

Author	Country of Study	Sample Size	Mean age/Median (SD/IQR)	% Female	Study Design	Treatment	Comparator	Follow-up Period	Dementia Type	MMSE at Baseline (SD)	Study Quality
Doody, 2008	US	31	72.1 (8.6)	45.2%	RCT	Donepezil 20 mg	Donepezil 10 mg + Placebo	24 weeks	AD	Standard dose: 20.9 (10-26) High dose: 22.1 (12-25)	Good
Doody, 2009	US	778	70.0 (10.0)	45.5%	RCT	Donepezil	Placebo	48 weeks	MCI	Donepezil: 328 (83.9) Placebo: 322 (83.2)	Good
Engedal, 2011	Norway and Sweden	89	74.6 (0.8)	57.3%	RCT	Galantamine fast titration	Galantamine slow titration	12 weeks	AD	20.3 (0.4)	Good

Author	Country of Study	Sample Size	Mean age/Median (SD/IQR)	% Female	Study Design	Treatment	Comparator	Follow-up Period	Dementia Type	MMSE at Baseline (SD)	Study Quality
Farlow, 2011	US	1434	73.9 (8.5)	62.8%	RCT	Donepezil 23 mg	Donepezil 10 mg	24 weeks	AD	Donepezil 10mg/d: 13.0 (4.75) Donepezil 23 mg/d: 13.1 (4.99)	Good
Fosbol, 2012	US and Denmark	76,233 (Medicare: 46,737 Danish: 29,496)	Medicare: 82 (77-87) Danish: 80 (76-84)	70.4%	Cohort	Any ChEI and Memantine	Donepezil	Medicare: 69.9 weeks (32.3-116.3) Danish: 133.6 weeks (63.4-223.7)	AD, LBW, PD	n/a	Good

Author	Country of Study	Sample Size	Mean age/Median (SD/IQR)	% Female	Study Design	Treatment	Comparator	Follow-up Period	Dementia Type	MMSE at Baseline (SD)	Study Quality
Gill, 2009	Canada	81,302	80.4 (7.1)	61.5%	Cohort	ChEIs	Control	104 weeks	Dementia (nonspecific)	n/a	Good
Hernandez, 2009	US	11,328	74.0 (11.4)	3.5%	Cohort	ChEIs	No treatment	104 weeks	Dementia (nonspecific)	n/a	Good
Herrmann, 2016	Canada	40	89.2 (3.5)	20.0%	RCT	ChEIs (continuation)	Placebo[3]	8 weeks	AD	8.1 (5.2)[4]	Fair
Isik, 2020	Turkey	57	80.77 (6.04)	63.2%	Cohort	9.5mg/24hr - 13.3 mg/24hr Rivastigmine patch	Baseline	4 weeks	LBD	15.77 (4.54)	Good
Kroger, 2012	The Netherlands	3,358	76.3 (7)	52.6%	Cohort	Rivastigmine, Galantamine or both	Unexposed period (patient as control)	464 weeks	AD	n/a	Good
Mohs, 2001	US	431	75.3 (0.6)	62.9%	RCT	Donepezil 5mg/d x28 days then 10 mg/day	Placebo	52 weeks	AD	17.1 (0.2)	Good

[3] Tapered off ChEI x2wk, then Placebo x6wk

[4] MMSE

Author	Country of Study	Sample Size	Mean age/Median (SD/IQR)	% Female	Study Design	Treatment	Comparator	Follow-up Period	Dementia Type	MMSE at Baseline (SD)	Study Quality
Nakamura, 2015	Japan	215	77.5 (6.21)	67.4%	RCT	1-step titration Rivastigmine patch	3-step titration Rivastigmine patch	24 weeks	AD	17.1 (2.74)	Good
Park-Wyllie, 2009	Canada	627	83 (5.4)	51.0%	Case-Control	ChEIs	Unexposed period (patient as control)	274 weeks	AD	n/a	Good
Raschetti, 2005	Italy	5,462	76 (7)	68.3%	Cohort	ChEIs[5]	Placebo	122 weeks	AD	18.2 (3.9)	Good
Sadowski, 2009	US	261	77.3 (8.04)	57.9%	RCT	4.6 mg/24 hr Rivastigmine patch (immediate vs delayed switch)	Baseline	25 weeks	AD	18.3 (3.99)	Good
San-Juan-Rodriguez, 2019	US	73,475	81.8 (8.3)	72.2%	Cohort	ChEIs inhibitor monotherapy	Memantine monotherapy; Combo of ChEIs inhibitor + memantine	156 weeks	AD	n/a	Good

[1] Low = Donepezil 5 mg, Rivastigmine ≤ 6 mg ,Galantamine ≤ 16 mg; High = Donepezil 10 mg, Rivastigmine > 6 mg, Galantamine > 16 mg

Author	Country of Study	Sample Size	Mean age/Median (SD/IQR)	% Female	Study Design	Treatment	Comparator	Follow-up Period	Dementia Type	MMSE at Baseline (SD)	Study Quality
Tariot, 2001	US	208	83.9 (28.4)	79.3%	RCT	Donepezil 10 mg	Placebo	24 weeks	AD	Placebo: 14.4 (5.8) Donepezil: 14.4 (5.4)	Good
Winblad, 2001	Denmark, Finland, Norway, Sweden and The Netherlands	286	72.5 (8.3)	64.3%	RCT	Donepezil 5 mg x 28 days then 10 mg qd	Placebo	52 weeks	AD	Donepezil: 19.37 (4.37) Placebo: 19.26 (4.54)	Good

Author	Country of Study	Sample Size	Mean age/Median (SD/IQR)	% Female	Study Design	Treatment	Comparator	Follow-up Period	Dementia Type	MMSE at Baseline (SD)	Study Quality
Wilkinson, 2003	US, Europe Canada and Australia	616	75.0 (0.3)	40.1%	RCT	Donepezil 5mg Donepezil 10mg	Placebo	24 weeks	VaD	Placebo: 22.2 (0.3) Donepezil 5mg/d: 21.8 (0.3) Donepezil 10 mg/d: 20.6 (0.7)	Good

DISCUSSION

This systematic review and meta-analysis of 25 studies involving 258,388 patients with ADRD demonstrated that ChEI use is associated with cardiovascular (CV) risks. In treated patients, both bradycardia and syncope occurred at clinically important absolute rates of approximately 5% and 10%, respectively. While the relative increases in risk were modest, they warrant careful consideration given the vulnerability of this population. Sensitivity analyses supported the robustness of these findings. These results have important implications for patient care, particularly regarding CV monitoring and risk assessment when initiating or continuing ChEI therapy.

The findings of this study are consistent with previous meta-analyses that have demonstrated increased risks of syncope and bradycardia following ChEI use.[18,55–57] These increased risks are biologically plausible, as ChEIs elevate acetylcholine levels in the brain to manage cognitive symptoms in patients with ADRD.[58] This same mechanism can lead to overstimulation of cholinergic receptors in the heart, resulting in increased vagal tone, which can cause bradycardia and hypotension.[58] Hypotension, in turn, may lead to syncope, especially in older adults who often have a diminished autonomic reserve and are more susceptible to CV side effects.[59,60] This biological pathway supports the findings of the meta-analysis, reinforcing the concern that ChEIs can pose significant CV risks in this vulnerable population. Point estimates from the sensitivity analysis continued to suggest increased risk, although one study changed the pooled estimate of the syncope risk.[8] This corroborates with the results from a previous meta-analysis of randomized controlled trials, which showed that excluding any single study did not materially affect the pooled odds ratios (OR) of increased risk of syncope, fall, and fracture.[61]

The absolute risk estimates of 5% for bradycardia and 9% for syncope are clinically meaningful and demand careful attention. In patients with ADRD, who are already vulnerable due to age and cognitive impairment, such increases in risk can lead to serious adverse outcomes. Syncope in older adults with dementia often results in falls, leading to fractures, hospitalizations, and a rapid decline in functional status. Similarly, bradycardia can necessitate discontinuing ChEIs or require interventions like pacemaker insertion,[6,8] particularly in patients with symptomatic bradycardia or underlying cardiac conduction abnormalities. These CV events not only impact patient safety and quality of life but also place additional burdens on caregivers and healthcare systems.

Given these findings, clinicians should carefully balance the cognitive benefits of ChEIs against their potential CV risks when treating patients with dementia. Regular monitoring for signs of bradycardia and syncope is essential, as early detection and intervention can mitigate adverse outcomes. If such symptoms occur, it may be necessary to reevaluate the use of ChEIs, considering dose reduction or discontinuation depending on the severity of the side effects. Additionally, educating patients and caregivers about recognizing these symptoms and knowing when to seek medical attention is critical for ensuring patient safety. The goal is to optimize cognitive function while minimizing harm, tailoring treatment strategies to each patient's CV profile and overall health status.

Heterogeneity, Sensitivity Analysis, and Publication Bias

To account for the observed heterogeneity, the meta-analysis employed random-effects modeling, which incorporates both within-study and between-study variability.[62] This approach ensures a more conservative and robust estimate of the pooled effect, recognizing that the true effect size may differ among studies and thereby enhancing the generalizability of the findings.[62]

Sensitivity analyses further supported the robustness of the results. For bradycardia, the findings remained consistent even when individual studies were omitted, indicating stability in the estimated effect. However, for syncope, the results were sensitive to the inclusion of the Gill study[8]; omitting this high-quality study affected the observed increase in relative risk. Therefore, its inclusion strengthens the reliability of the results.

The assessment of publication bias revealed nuanced findings. For bradycardia, there was no significant evidence of publication bias, supporting the reliability of the risk estimates. In contrast, the results for syncope suggested potential concerns. While Egger's test did not indicate significant bias, Begg's test suggested possible funnel plot asymmetry, implying some degree of publication bias. The trim-and-fill method revealed higher adjusted estimates for syncope than those in the primary analysis, suggesting that the initial analysis may have underestimated the true risk associated with ChEIs.[63] This underscores the need for clinicians to monitor patients closely for syncope, as the risk may be greater than previously anticipated.

Strengths and Limitations

This study provides centralized evidence on the risk of bradycardia and syncope associated with ChEI use, enhancing previous analyses by emphasizing absolute risks in the exposed group. Estimating and reporting absolute risks, which were not in previous studies offers clinically meaningful insights, as it allows clinicians to interpret RR and OR within the context of actual

event rates. This is crucial because a low absolute risk may render even a large increase in RR or OR clinically insignificant, while a high absolute risk can make a small increase clinically important.[64,65]

The interpretation of these study findings must consider several limitations. First, although this systematic review included studies investigating bradycardia and syncope in non-Alzheimer's dementias (such as vascular dementia and Parkinson's disease), the primary studies often did not report results separately by dementia subtype. This lack of stratified data precluded our ability to estimate risks specific to each type of dementia. Second, we could not ascertain the impact of certain co-prescribed medications, such as antipsychotics, antihypertensives, and antidepressants, on the findings because some included studies did not adjust for these variables in their analyses. Finally, the study did not assess the specific contributions of individual ChEIs due to limited and inconsistent reporting.

CONCLUSION

This systematic review and meta-analysis demonstrated an association between ChEI use and an increased risk of syncope and bradycardia in patients with ADRD. The findings support current guideline recommendations for careful CV monitoring of patients taking ChEIs. Clinicians should balance the cognitive benefits of these medications against the potential for CV adverse events, incorporating these considerations into shared decision-making with patients and caregivers. Future research should explore individual ChEI effects and patient-specific factors to refine risk assessment and personalize treatment strategies.

References

1. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health*. 2022;7(2):e105–e125. doi:10.1016/S2468-2667(21)00249-8
2. Parsons C, Briesacher BA, Givens JL, Chen Y, Tjia J. Cholinesterase inhibitor and memantine use in newly admitted nursing home residents with dementia. *J Am Geriatr Soc*. 2011;59(7):1253-1259. doi:10.1111/j.1532-5415.2011.03478.x
3. Masuda Y. Cardiac effect of cholinesterase inhibitors used in Alzheimer's disease–from basic research to bedside. *Curr Alzheimer Res*. 2004;1(4):315-321. doi:10.2174/1567205043332009
4. Mosqueda-Garcia R, Furlan R, Tank J, Fernandez-Violante R. The elusive pathophysiology of neurally mediated syncope. *Circulation*. 2000;102(23):2898-2906. doi:10.1161/01.cir.102.23.2898
5. 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(9):867-873. doi:10.1001/archinternmed.2009.43
6. Gill SS, Mamdani M, Naglie G, et al. A prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs. *Arch Intern Med*. 2005;165(7):808-813. doi:10.1001/archinte.165.7.808
7. Rochon P GJNSNMGSS. Prescribing Cascade in a Cardiology Practice. https://www.acc.org/latest-in-cardiology/articles/2018/01/08/10/43/prescribing-cascade-in-a-cardiology-practice.
8. Gill SS, Anderson GM, Fischer HD, et al. *Syncope and Its Consequences in Patients With Dementia Receiving Cholinesterase Inhibitors A Population-Based Cohort Study*. https://jamanetwork.com/
9. Rogers SL, Doody RS, Mohs RC, Friedhoff LT. Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. Donepezil Study Group. *Arch Intern Med*. 1998;158(9):1021-1031. doi:10.1001/archinte.158.9.1021
10. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. *Neurology*. 1998;50(1):136-145. doi:10.1212/wnl.50.1.136
11. Pitrou I, Boutron I, Ahmad N, Ravaud P. Reporting of safety results in published reports of randomized controlled trials. *Arch Intern Med*. 2009;169(19):1756-1761. doi:10.1001/archinternmed.2009.306
12. Tsang R, Colley L, Lynd LD. Inadequate statistical power to detect clinically significant differences in adverse event rates in randomized controlled trials. *J Clin Epidemiol*. 2009;62(6):609-616. doi:10.1016/j.jclinepi.2008.08.005
13. Bordier P, Lanusse S, Garrigue S, et al. Causes of syncope in patients with Alzheimer's disease treated with donepezil. *Drugs Aging*. 2005;22(8):687-694. doi:10.2165/00002512-200522080-00005
14. Bordier P, Colsy M, Robert F, Bourenane G. Prevalence of positive carotid sinus massage and related risk of syncope in patients with Alzheimer's disease. *Europace*. 2007;9(9):829-834. doi:10.1093/europace/eum148
15. Hernandez RK, Farwell W, Cantor MD, Lawler E V. Cholinesterase inhibitors and incidence of

bradycardia in patients with dementia in the veterans affairs new England healthcare system. *J Am Geriatr Soc*. 2009;57(11):1997-2003. doi:10.1111/j.1532-5415.2009.02488.x
16. Syncope with cholinesterase inhibitors. *Prescrire Int*. 2011;20(120):240.
17. Kim DH, Brown RT, Ding EL, Kiel DP, Berry SD. Dementia medications and risk of falls, syncope, and related adverse events: meta-analysis of randomized controlled trials. *J Am Geriatr Soc*. 2011;59(6):1019-1031. doi:10.1111/j.1532-5415.2011.03450.x
18. Isik AT, Soysal P, Stubbs B, et al. Cardiovascular Outcomes of Cholinesterase Inhibitors in Individuals with Dementia: A Meta-Analysis and Systematic Review. *J Am Geriatr Soc*. 2018;66(9):1805-1811. doi:10.1111/jgs.15415
19. Kose E, Yamamoto T, Tate N, Ando A, Enomoto H, Yasuno N. Adverse Drug Event Profile Associated with Anti-dementia Drugs: Analysis of a Spontaneous Reporting Database. *Pharmazie*. 2023;78(5):42-46. doi:10.1691/ph.2023.2584
20. San-Juan-Rodriguez A, Zhang Y, He M, Hernandez I. Association of Antidementia Therapies With Time to Skilled Nursing Facility Admission and Cardiovascular Events Among Elderly Adults With Alzheimer Disease. *JAMA Netw Open*. 2019;2(3):e190213. doi:10.1001/jamanetworkopen.2019.0213
21. Tenia Slade OWIYunusa. Risk of bradycardia and syncope associated with the use of cholinesterase inhibitors: protocol for systematic review and meta-analysis. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022308730.
22. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71
23. Kamali F. *Hypotension and Syncope*. 2nd ed. (Maleki M, Alizadehasl A, Haghjoo M, eds.). Practical Cardiology; 2022.
24. American Heart Association. Bradycardia: Slow Heart Rate. https://www.heart.org/en/health-topics/arrhythmia/about-arrhythmia/bradycardia--slow-heart-rate.
25. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev*. 2016;5(1):210. doi:10.1186/s13643-016-0384-4
26. National Heart, Lung, and Blood Institute. Study Quality Assessment Tools. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.
27. Tanriver-Ayder E, Faes C, Van De Casteele T, McCann SK, Macleod MR. Comparison of commonly used methods in random effects meta-analysis: Application to preclinical data in drug discovery research. *BMJ Open Science*. 2021;5(1). doi:10.1136/bmjos-2020-100074
28. West SL, Gartlehner G, Mansfield AJ. Comparative Effectiveness Review Methods: Clinical Heterogeneity. In: *Summary of Common Statistical Approaches to Test for Heterogeneity*. https://www.ncbi.nlm.nih.gov/books/NBK53317/table/ch3.t2/; 2010.
29. Lin L, Chu H. Quantifying publication bias in meta-analysis. *Biometrics*. 2018;74(3):785-794. doi:10.1111/biom.12817
30. Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ (Online)*. 2011;343(7818). doi:10.1136/bmj.d4002
31. Willis BH, Riley RD. Measuring the statistical validity of summary meta-analysis and meta-regression results for use in clinical practice. *Stat Med*. 2017;36(21):3283-3301. doi:10.1002/sim.7372
32. Burns A, Gauthier S, Perdomo C. Efficacy and safety of donepezil over 3 years: An open-label, multicentre study in patients with Alzheimer's disease. *Int J Geriatr Psychiatry*. 2007;22(8):806-812. doi:10.1002/gps.1746

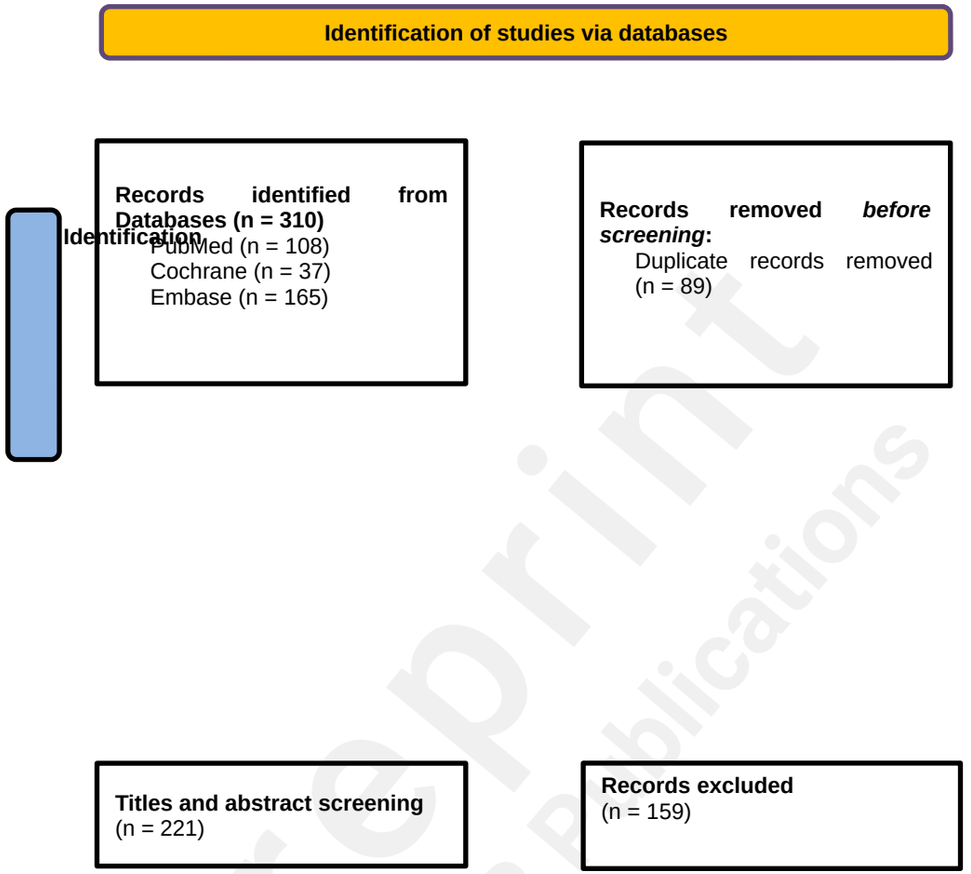
33. Black S, Román GC, Geldmacher DS, et al. Efficacy and tolerability of donepezil in vascular dementia: Positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. *Stroke*. 2003;34(10):2323-2330. doi:10.1161/01.STR.0000091396.95360.E1
34. Campbell NL, Perkins AJ, Gao S, et al. Adherence and Tolerability of Alzheimer's Disease Medications: A Pragmatic Randomized Trial. *J Am Geriatr Soc*. 2017;65(7):1497-1504. doi:10.1111/jgs.14827
35. Barone P, Burn DJ, van Laar T, Hsu C, Poewe W, Lane RM. Rivastigmine versus placebo in hyperhomocysteinemic Parkinson's disease dementia patients. *Movement Disorders*. 2008;23(11):1532-1540. doi:10.1002/mds.21997
36. Kröger E, Berkers M, Carmichael PH, Souverein P, Van Marum R, Egberts T. Use of rivastigmine or galantamine and risk of adverse cardiac events: A database study from the netherlands. *American Journal of Geriatric Pharmacotherapy*. 2012;10(6):373-380. doi:10.1016/j.amjopharm.2012.11.002
37. Fosbøl EL, Peterson ED, Holm E, et al. Comparative cardiovascular safety of dementia medications: A cross-national study. *J Am Geriatr Soc*. 2012;60(12):2283-2289. doi:10.1111/j.1532-5415.2012.04241.x
38. Park-Wyllie LY, Mamdani MM, Li P, Gill SS, Laupacis A, Juurlink DN. Cholinesterase inhibitors and hospitalization for bradycardia: A population-based study. *PLoS Med*. 2009;6(9). doi:10.1371/journal.pmed.1000157
39. Doody RS, Corey-Bloom J, Zhang R, Li H, Ieni J, Schindler R. *Safety and Tolerability of Donepezil at Doses up to 20 Mg/Day Results from a Pilot Study in Patients with Alzheimer's Disease*. Vol 25.; 2008.
40. Engedal K, Davis B, Richarz U, Han J, Schäuble B, Andreasen N. Two galantamine titration regimens in patients switched from donepezil. *Acta Neurol Scand*. 2012;126(1):37-44. doi:10.1111/j.1600-0404.2011.01594.x
41. Mohs RC, Doody ; R S, Morris ; J C, et al. *A 1-Year, Placebo-Controlled Preservation of Function Survival Study of Donepezil in AD Patients*.; 2001.
42. Farlow M, Veloso F, Moline M, et al. *Safety and Tolerability of Donepezil 23 Mg in Moderate to Severe Alzheimer's Disease*.; 2011. http://www.biomedcentral.com/1471-2377/11/57
43. Doody RS, Ferris SH, Salloway S, et al. *Donepezil Treatment of Patients with MCI A 48-Week Randomized, Placebo-Controlled Trial Background: Treatment of Mild Cognitive Impairment (MCI) with Cholinesterase Inhibitors May*.; 2009. www.neurology.org.
44. Raschetti R, Maggini M, Sorrentino GC, Martini N, Caffari B, Vanacore N. A cohort study of effectiveness of acetylcholinesterase inhibitors in Alzheimer's disease. *Eur J Clin Pharmacol*. 2005;61(5-6):361-368. doi:10.1007/s00228-005-0946-1
45. Bordier P, Garrigue S, Lanusse S, et al. *Cardiovascular Effects and Risk of Syncope Related to Donepezil in Patients with Alzheimer's Disease*. Vol 20.; 2006.
46. Isik AT, Ates Bulut E, Dokuzlar O, et al. *Cardiac and Blood Pressure Safety of Transdermal Rivastigmine in Elderly Patients With Dementia With Lewy Bodies*.; 2020. www.alzheimerjournal.com
47. Wilkinson D, Murray J. Galantamine: A randomized, double-blind, dose comparison in patients with Alzheimer's disease. *Int J Geriatr Psychiatry*. 2001;16(9):852-857. doi:10.1002/gps.409
48. Tariot PN, Solomon ; P R, Morris ; J C, Kershaw ; P, Lilienfeld ; S. *A 5-Month, Randomized, Placebo-Controlled Trial of Galantamine in AD*.; 2269.
49. Nakamura Y, Strohmaier C, Tamura K, et al. A 24-Week, Randomized, Controlled Study to

Evaluate the Tolerability, Safety and Efficacy of 2 Different Titration Schemes of the Rivastigmine Patch in Japanese Patients with Mild to Moderate Alzheimer's Disease. *Dement Geriatr Cogn Dis Extra*. 2015;5(3):361-374. doi:10.1159/000439269

50. Sadowsky CH, Dengiz A, Olin JT, Koumaras B, Meng X, Brannan S. Switching from donepezil tablets to rivastigmine transdermal patch in alzheimer's disease. *Am J Alzheimers Dis Other Demen*. 2009;24(3):267-275. doi:10.1177/1533317509333037
51. Winblad B, Engedal ; K, Soininen ; H, et al. *A 1-Year, Randomized, Placebo-Controlled Study of Donepezil in Patients with Mild to Moderate AD and the Donepezil Nordic Study Group*.*; 2001. www.neurology.org
52. San-Juan-Rodriguez A, Zhang Y, He M, Hernandez I. Association of Antidementia Therapies With Time to Skilled Nursing Facility Admission and Cardiovascular Events Among Elderly Adults With Alzheimer Disease. *JAMA Netw Open*. 2019;2(3):e190213. doi:10.1001/jamanetworkopen.2019.0213
53. Herrmann N, O'Regan J, Ruthirakuhan M, et al. A Randomized Placebo-Controlled Discontinuation Study of Cholinesterase Inhibitors in Institutionalized Patients With Moderate to Severe Alzheimer Disease. *J Am Med Dir Assoc*. 2016;17(2):142-147. doi:10.1016/j.jamda.2015.08.019
54. Burns A, Bernabei R, Bullock R, et al. Articles Safety and effi cacy of galantamine (Reminyl) in severe Alzheimer's disease (the SERAD study): a randomised, placebo-controlled, double-blind trial. *Lancet Neurol*. 2009;8:39-47. doi:10.1016/S1474
55. Ahuja M, Siddhpuria S, Karimi A, et al. Cholinesterase inhibitors and falls, syncope and injuries in patients with cognitive impairment: a systematic review and meta-analysis. *Age Ageing*. 2023;52(11). doi:10.1093/ageing/afad205
56. Kim DH, Brown RT, Ding EL, Kiel DP, Berry SD. Dementia medications and risk of falls, syncope, and related adverse events: Meta-analysis of randomized controlled trials. *J Am Geriatr Soc*. 2011;59(6):1019-1031. doi:10.1111/j.1532-5415.2011.03450.x
57. Buckley JS, Salpeter SR. A Risk-Benefit Assessment of Dementia Medications: Systematic Review of the Evidence. *Drugs Aging*. 2015;32(6):453-467. doi:10.1007/s40266-015-0266-9
58. Yaari R, Tariot PN, Schneider LS. Cognitive Enhancers and Treatments for Alzheimer's Disease. In: *Psychiatry*. Wiley; 2008:2294-2317. doi:10.1002/9780470515167.ch107
59. Grubb BP. Pathophysiology and differential diagnosis of neurocardiogenic syncope11This article may contain discussion of off-label or investigational uses (not yet approved by the FDA) of various therapeutic agents. Please refer to the box provided on page 2Q of this supplement for a disclosure of such agents. *Am J Cardiol*. 1999;84(8):3-9. doi:10.1016/S0002-9149(99)00691-8
60. Forman DE, Lipsitz LA. SYNCOPE IN THE ELDERLY. *Cardiol Clin*. 1997;15(2):295-311. doi:10.1016/S0733-8651(05)70337-4
61. Kim DH, Brown RT, Ding EL, Kiel DP, Berry SD. Dementia medications and risk of falls, syncope, and related adverse events: Meta-analysis of randomized controlled trials. *J Am Geriatr Soc*. 2011;59(6):1019-1031. doi:10.1111/j.1532-5415.2011.03450.x
62. Dettori JR, Norvell DC, Chapman JR. Fixed-Effect vs Random-Effects Models for Meta-Analysis: 3 Points to Consider. *Global Spine J*. 2022;12(7):1624-1626. doi:10.1177/21925682221110527
63. Mavridis D, Salanti G. How to assess publication bias: funnel plot, trim-and-fill method and selection models. *Evidence Based Mental Health*. 2014;17(1):30-30. doi:10.1136/eb-2013-101699
64. Louik C, Lin AE, Werler MM, Hernández-Díaz S, Mitchell AA. First-Trimester Use of Selective

Serotonin-Reuptake Inhibitors and the Risk of Birth Defects. *New England Journal of Medicine*. 2007;356(26):2675-2683. doi:10.1056/NEJMoa067407

65. Andrade C. Understanding Relative Risk, Odds Ratio, and Related Terms: As Simple as It Can Get. *J Clin Psychiatry*. 2015;76(07):e857-e861. doi:10.4088/JCP.15f10150



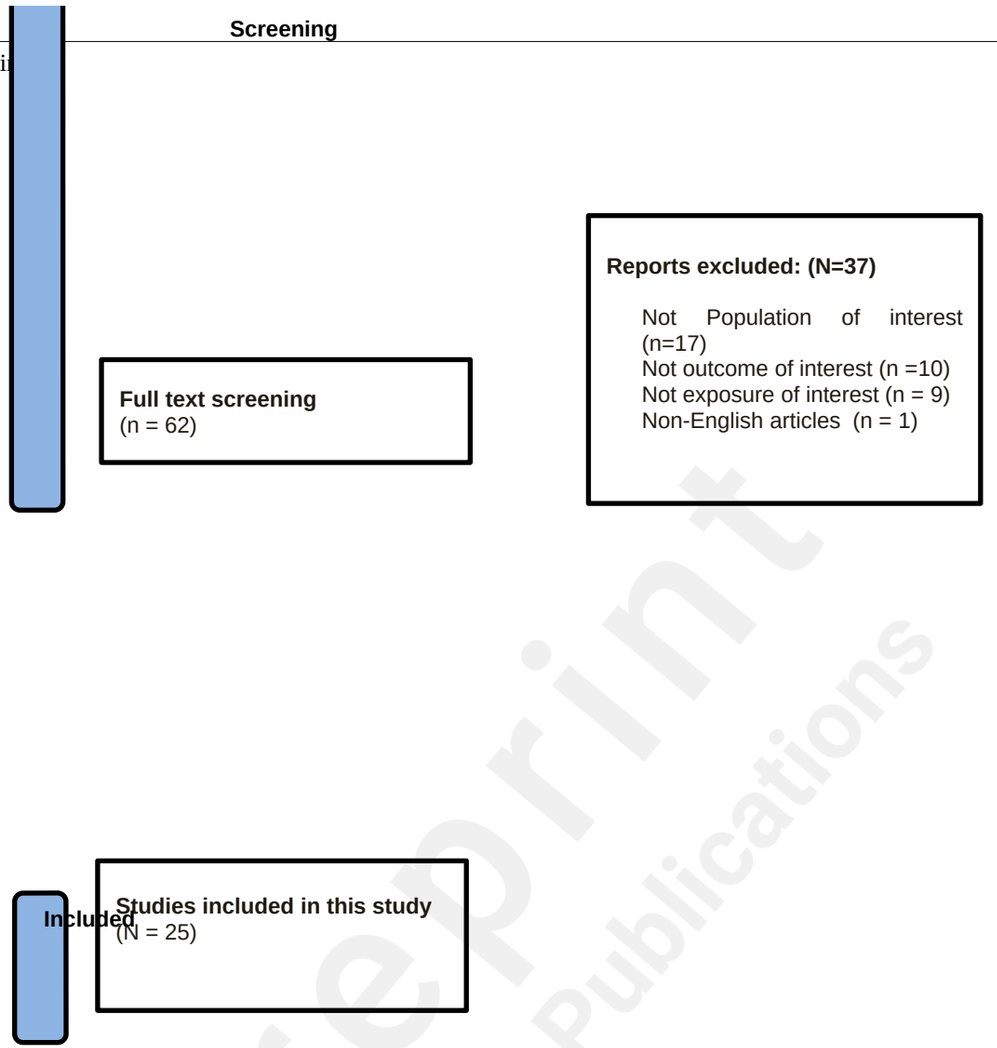


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram of literature search and selection.[21] For more information, visit: http://www.prisma-statement.or

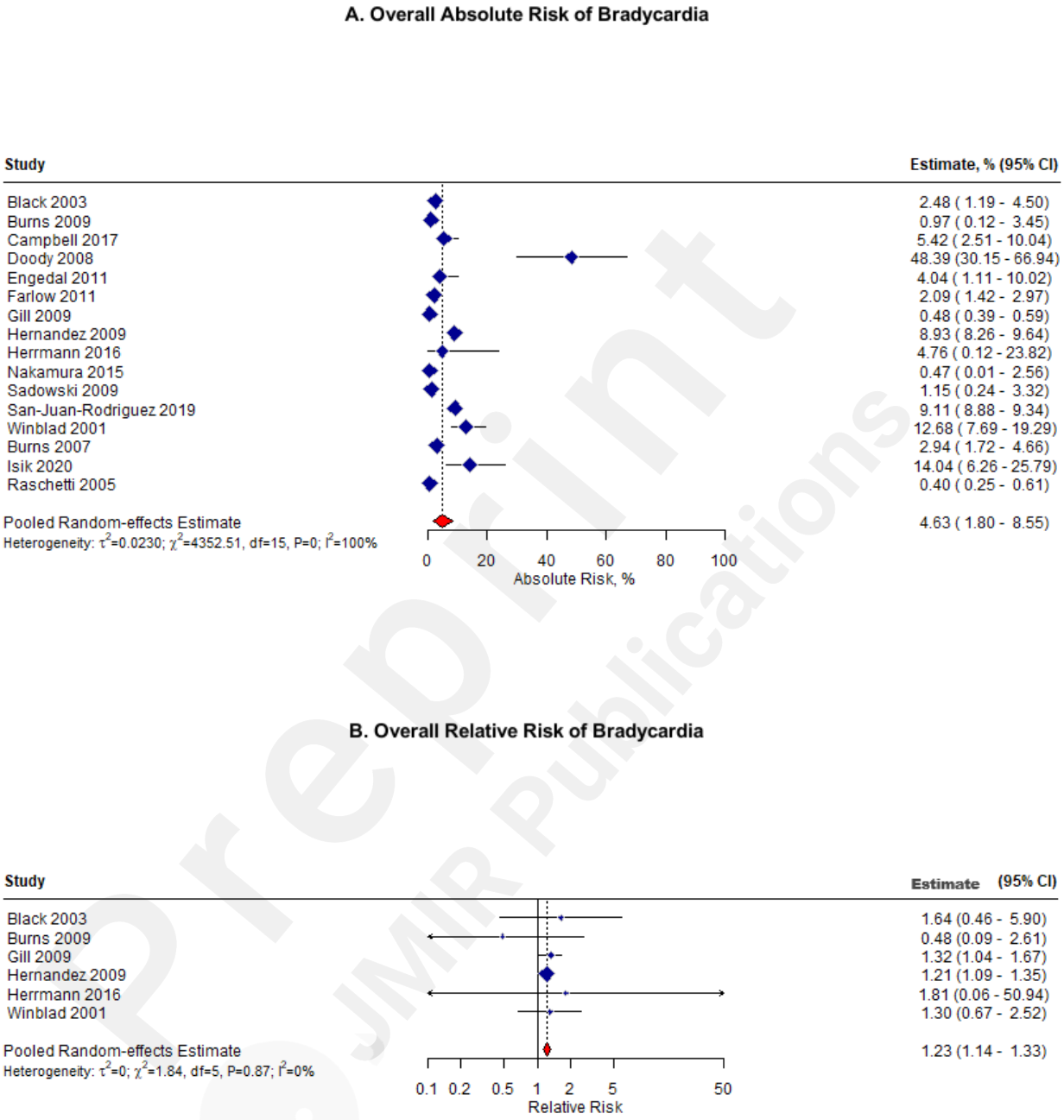


Fig 2A: Random effect meta-analysis of the association between ChEI use and the absolute /cumulative risk of bradycardia among exposed patients
Fig 2B: Random effect meta-analysis of the association between ChEI use and the relative risk of bradycardia

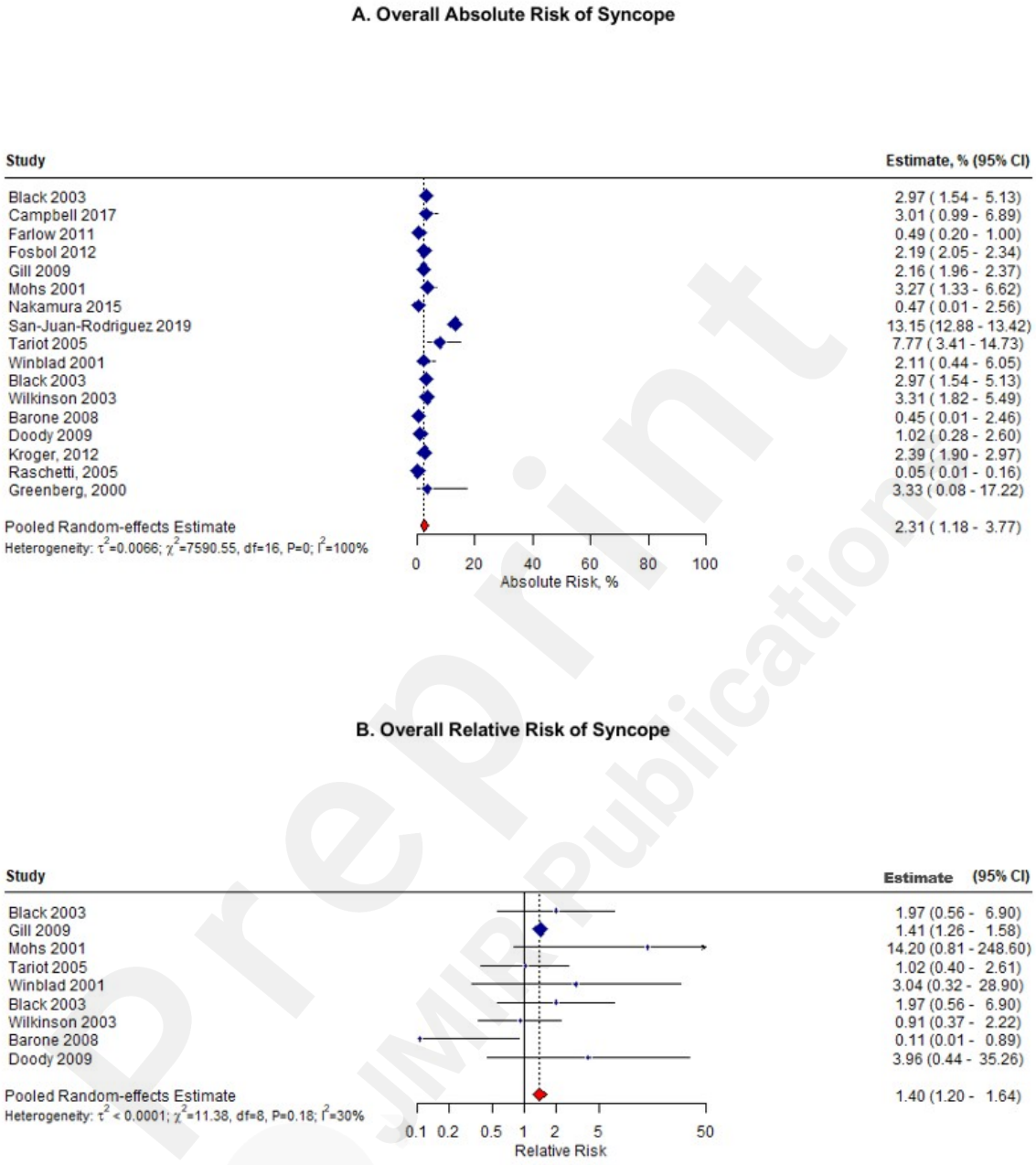


Fig 3A: Random effect meta-analysis of the association between ChEI use and the absolute /cumulative risk of syncope among exposed patients
Fig 3B: Random effect meta-analysis of the association between ChEI use and the relative risk of syncope

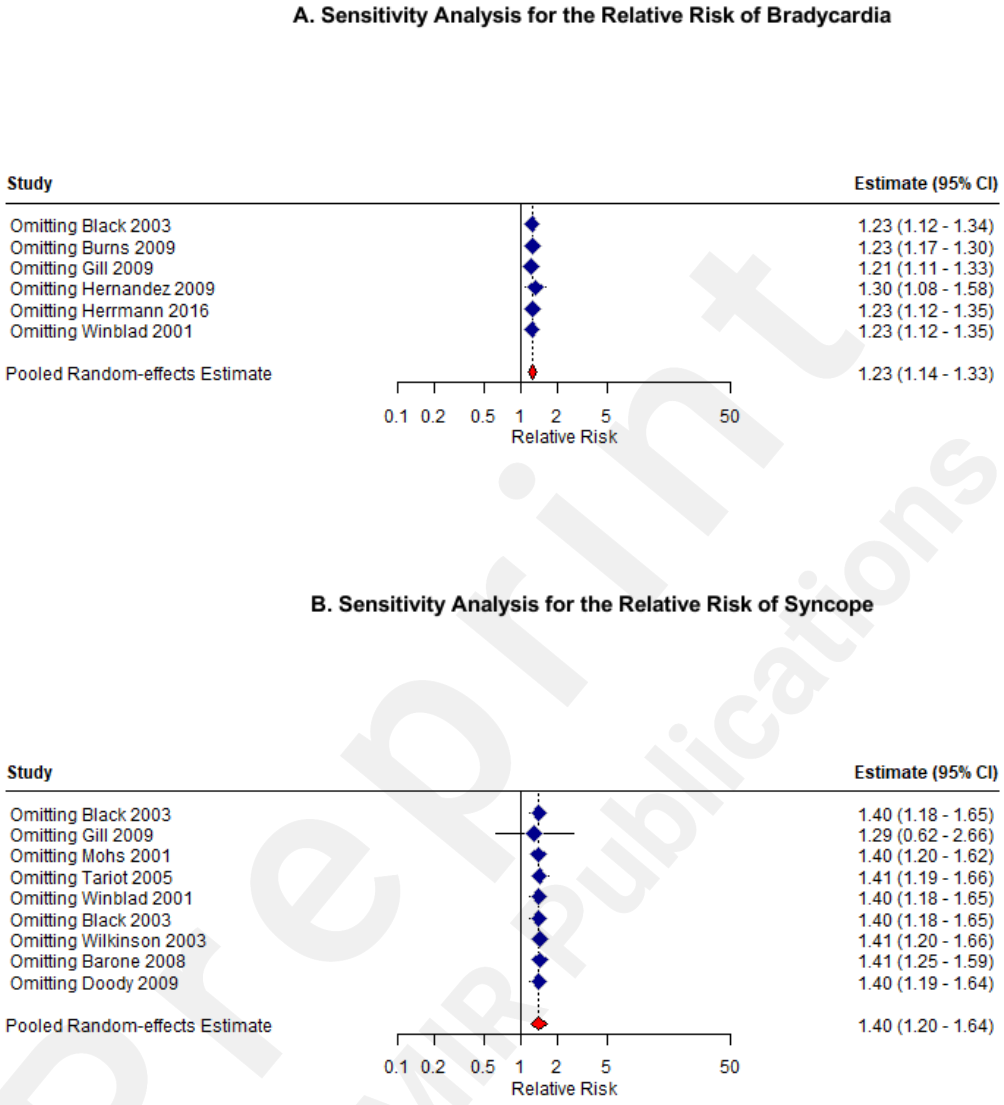


Fig 4A: One-study removal sensitivity analysis of the association between ChEI use and the relative risk of bradycardia

Fig 4B: One-study removal sensitivity analysis of the association between ChEI use and the relative risk of syncope

Supplementary Files

Multimedia Appendixes

PRISMA diagram.
URL: http://asset.jmir.pub/assets/14aa7ccd063f8c763072da94ec06f6a5.docx