Antiplatelet therapy and incident cognitive impairment or dementia-a systematic review and meta-analysis of randomised clinical trials

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SYSTEMATIC REVIEW

Antiplatelet therapy and incident cognitive impairment or dementia—a systematic review and meta-analysis of randomised clinical trials

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Abstract

Objective: The benefit of antiplatelet therapy in preventing cognitive impairment or dementia is uncertain. We investigated the association between antiplatelet therapy and incident cognitive impairment or dementia in randomised clinical trials.
Methods: We searched PubMed, EMBASE and CENTRAL for randomised clinical trials published from database inception through 1 February 2023. Trials that evaluated the association of antiplatelet therapy with incident cognitive impairment or dementia were included. For single-agent antiplatelet, the control group was placebo. For dual agent antiplatelet therapy, the control group was single-agent monotherapy. A random-effects meta-analysis model was used to report pooled treatment effects and 95% confidence intervals (CIs). The primary outcome was incident cognitive impairment or dementia. Secondary outcomes included change in cognitive test scores.
Results: A total of 11 randomised clinical trials were included (109,860 participants). All reported the incidence of cognitive impairment or dementia on follow-up. The mean (SD) age of trial participants was 66.2 (7.9) years. Antiplatelet therapy was not significantly associated with a reduced risk of cognitive impairment or dementia (11 trials; 109,860 participants) (3.49% versus 4.18% of patients over a mean trial follow-up of 5.8 years; odds ratio [OR], 0.94 [95% CI, 0.88–1.00]; absolute risk reduction, 0.2% [95% CI, −0.4% to 0.009%]; $I2 = 0.0\%$). Antiplatelet therapy was not significantly associated with mean change in cognitive test scores.
Conclusion: In this meta-analysis, antiplatelet therapy was not significantly associated with a lower risk of incident cognitive impairment or dementia, but the CIs around this outcome do not exclude a modest preventative effect.

Keywords: Dementia, Cognitive impairment, Antiplatelet therapy, Dementia prevention, Systematic Review, Older people

Key Points

- Antiplatelet therapy compared with control was not significantly associated with a lower risk of cognitive impairment or dementia.
- The confidence intervals for this outcome do not preclude a modest treatment benefit (up to 12% risk reduction).
- A modest effect in such a cheap and ubiquitous medication could have a large effect at a population level.
- A standardised set of cognitive outcomes and long-term follow-up are both needed in future dementia prevention trials.
- Antiplatelet therapy does not appear to have any effect on cognitive test scores.

Introduction

Cognitive impairment and dementia are a major cause of morbidity and mortality worldwide, with about 6% of the world's population above the age of 50 living with cognitive impairment [1]. Identifying population-level interventions to reduce the burden of dementia is a public health priority.

Vascular disease is a major contributor to the pathogenesis of cognitive impairment and dementia, and can manifest through atherosclerosis of the vasculature supplying the brain, or due to the impact of co-morbid cardiovascular conditions [2]. While there is a substantial evidence-base for the benefit of antiplatelet therapy for secondary prevention of major vascular events (e.g. ischemic stroke and myocardial infarction), there is uncertainty about the benefit for antiplatelet therapy on cognitive decline [3]. The benefits of secondary prevention with antiplatelet therapy must also be balanced with the risk of intracerebral bleeding, including micro-bleeding [4, 5].

Evaluating the association of preventative cardiovascular therapies with cognitive decline requires large sample sizes with extended duration of follow-up, because treatment effects are usually modest (e.g. antihypertensive therapy) and the cause–effect relationship of covert vascular disease and dementia observes a long latency period [6]. However, given the global burden of cognitive impairment and dementia, even a modest relative risk reduction associated with antiplatelet therapy may have substantial benefits at a population-level in reducing dementia prevalence and associated healthcare costs [7].

A meta-analysis was performed to determine whether the use of antiplatelet therapy was associated with the incidence of cognitive impairment or dementia.

Methods

We performed a systematic review and meta-analysis and reported our findings according to the standards described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [8]. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42022315855).

Search strategy and selection criteria

We developed the search strategy, without language restriction, for PubMed, EMBASE and CENTRAL for articles published from database inception to 1 February 2023. The reference list of studies selected for inclusion and published systematic reviews of antiplatelet trials were screened for studies that met our inclusion criteria. The search terms included dementia, cognitive impairment, the names of common cognitive tests, the word antiplatelet and different antiplatelet generic and brand names and randomised clinical trials. The search strategy was peer-reviewed by a second information specialist. The full search strategy is included in the Supplement (Supplementary Methods S1). Two reviewers (K.K and R.M.) independently screened titles and abstracts. Full texts were sourced for relevant articles. Inclusion criteria were assessed independently, and inconsistencies were resolved by consensus.

Trials were eligible if they were randomised, compared antiplatelet with a control, had at least 1 year of follow-up, included more than 500 participants and reported on the prespecified outcomes which included: cognitive impairment, dementia or change in cognitive scores. Clinical trials that compared either antiplatelet monotherapy with control, or dual antiplatelet therapy to monotherapy were eligible. For dual antiplatelet trials, we required that one of the antiplatelet agents was common to both arms of the trial (i.e. A versus A + B) to ensure measurement of an independent antiplatelet agent effect. Trials that investigated the effect of antiplatelets on people with a prior diagnosis of dementia, and trials that investigated a single antiplatelet versus a different single antiplatelet were excluded. These eligibility criteria were designed to allow the inclusion of a broad range of indications for antiplatelet therapy, as we felt that if an association was present, it would likely be a modest reduction.

Data extraction

Two authors (K.K. and R.M.) independently extracted data into a dedicated database based on an agreed list of key study characteristics and outcomes. This included baseline demographics of participants, study characteristics, the intervention antiplatelet regimen and the comparator, definition of cognitive impairment or dementia used, incidence of dementia or cognitive impairment and change in cognitive score. We reported outcomes from the point of longest available follow-up [9]. Data were primarily extracted from the main manuscript paper, and if not present in the main manuscript or supplementary appendix we completed a targeted search of reported outcomes of cognitive impairment or dementia from ClinicalTrials.gov. We defined primary prevention trials as those in which more than 50% of all participants had no history of cardiovascular events.

Outcomes

The primary outcome of this meta-analysis was cognitive impairment or dementia. We combined diagnoses of cognitive impairment and dementia in our analysis to maximise the number of available clinical trials. As cognitive impairment and dementia represent a spectrum of the same neurocognitive syndrome, our hypothesis was that any consistent reduction in incidence should be present for both conditions. Definition of dementia was based on a composite of cognitive score and established criterion in two trials [10, 11] (based on the Diagnostic and Statistical Manual of Mental Disorders criteria and the International Classification of Diseases criteria), clinically determined in four trials [12–15], based purely on cognitive scoring in four trials

[16–19] and on prescription of 'anti-dementia' medication or requirement for nursing home care in one trial [20]. The secondary outcome was change in mean cognitive scores, expressed as a continuous variable. We included cognitive test scores that were most common to multiple trials or could be converted to a common score using validated conversion tables and then meta-analysed ($n = 3$). We also used global cognitive scores reported by several of our included studies ($n = 4$), which were expressed as a Z-score and suitable for meta-analysis.

Risk of bias assessment

We used version 2 of the Cochrane risk of bias tool to assess methodological quality of eligible trials [21]. Trials were assessed on random sequence generation, allocation concealment, blinding of participants and health care personnel, blinded outcome assessment, completeness of outcome data, evidence of selective reporting and other biases. Two independent reviewers (K.K. and A.C.) performed risk of bias assessments, and disagreements were resolved by a third reviewer (R.M.). If one of the previously mentioned domains were rated as high risk, the study was at a high risk of bias.

Data synthesis and analysis

A descriptive analysis of all included trials is reported in Table 1 and Supplementary Table S1. For dichotomous outcomes (presence or absence of cognitive impairment or dementia), odds ratios (ORs) and 95% confidence intervals (CIs) were estimated from each trial. Weighted pooled treatment effects were calculated using a random-effects meta-analysis model. For cognitive score continuous outcomes, e.g. Mini-Mental State Examination (MMSE) score, the mean change from baseline score to follow-up was used. Where standard error was reported, standard deviations were obtained from the standard error by multiplying by the square root of the sample size using the following formula: $SD = SE \times \sqrt{n}$ [21]. Four trials reported a global cognitive score [10, 11, 16, 18], representing a composite of individual cognitive scores, represented as a Z-score. Z-scores from the separate trials were also pooled using a random-effects meta-analysis model. We utilised validated scales [22–24] that converted cognitive scores (3MSE, TICS, MOCA) to their MMSE equivalent score and performed a pooled mean difference and 95% CI using a random-effects meta-analysis. As we did not have individual level data, we created a simulation dataset of the reported cognitive scores, of size n, with mean μ and SD σ using rnorm in R. Using 3MSE as an example, the n, μ and σ were selected from the distribution of the 3MSE score. Each simulated 3MSE was then converted to an MMSE score using lookup tables [22–24]. We then repeated this with a parametric bootstrap to estimate the mean and SD of the converted MMSE score and used this in our meta-analysis. This process was then repeated for conversion of MOCA and TICS scores to MMSE. As change from baseline standard deviation scores was not reported for any of our cognitive scores, standard deviation was imputed using a correlation coefficient of 0.8 [21]. For the additional cognitive test scores which were expressed as Z scores, we calculated a pooled mean standardised difference (Cohen's d) using a random effects meta-analysis model. Heterogeneity across studies was investigated using forest plots and I^2 statistics. A priori subgroup sensitivity analyses were performed to assess pooled estimates for trials that reported incident cognitive impairment or dementia rates above and below the median age, above and below the average number of female participants, single antiplatelet trials versus dual antiplatelet trials, primary versus secondary prevention trials, by the source of data for the outcome—primary publication versus ClinicalTrials.gov and by less or more than 100 months of follow-up. We tested for an interaction between subgroup relative risks by dividing the difference in log relative risk by its standard error. Statistical analyses were performed using the Metafor package for R. Comparisons were two-tailed using a threshold of $P \leq 0.5$ for significance for all analyses except for subgroup interactions, where we used a threshold of $P \leq 0.10$ for significance [25].

Results

Our search strategy performed on the 1 February 2023 identified 5,402 articles. After title and abstract screening, 47 articles were considered potentially relevant, of which 11 were included after full text review (Supplementary Figure S1). A total of 11 studies reported the incidence of a composite of cognitive impairment or dementia ($n = 11$) on follow-up and were included in the primary meta-analysis [10–20]. Four studies reported mean change of a cognitive score [10, 11, 16, 18]. Three studies [10, 16, 19] provided cognitive scores which were converted to MMSE for pooled analysis.

Study characteristics

Overall, 109,860 participants were included from 11 trials, with a mean (standard deviation) age of trial participants of 66.2 (7.9) years and 51% were women. The mean (range) duration of follow-up was 70 months (33–136) months, with 656,207 participant years of follow-up (Table 1). The publication year ranged from 2008 to 2023. Eight of the trials included a primary prevention population [10, 11, 14–17, 19, 20], and three trials included a secondary prevention population [12, 13, 18]. One of the trials was of a post-stroke population [18], and two trials included participants with a history of cardiovascular disease [12, 13]. A total of 10 trials were placebo controlled [10–19], and in one trial, the intervention was compared with usual care [20]. Seven of the included trials investigated single antiplatelet therapy [10, 11, 14, 16, 17, 19, 20], and the other four investigated dual antiplatelet therapy [12, 13, 15, 18] (Supplementary Table S1). We extracted rates of these cognitive outcomes from the original publication in seven trials [10, 11, 16–20], and from searching ClinicalTrials.gov in four trials [12–15].

Table 1. Participant characteristics of included studies in the analysis of incident cognitive impairment or dementia

Trial, year	No. of participants	Mean age	Female participants, no. (%)	Cognitive test used at baseline	Mean or median baseline cognitive score – Intervention (SD)	Mean or median baseline cognitive score - Control (SD)
WHS, 2007 [16]	6,377	66.2	6,377 (100)	TICS[a]	34.2 (4–41)	34.3 (15–41)
AAA, 2008 [17]	2,309	62	1,686 (73)	Mill Hill vocabulary scale score[b]	30.9 (4.7)	31.1 (4.7)
ACTIVE A, 2009 [15]	7,554	70	3,157 (41.8)	Not reported	Not reported	Not reported
SPS3, 2014 [18]	2,668	63	1,001 (37.5)	CASI z-score[c]	−0.63 (1.47)	−0.56 (1.39)
PEGASUS-TIMI, 2015 [13]	21,162	65.3	5,060 (23.9)	Not reported	Not reported	Not reported
ARRIVE, 2018 [14]	12,546	63.9	3,708 (29.5)	Not reported	Not reported	Not reported
JPAD. 2019 [20]	2,536	65	1,150 (45.3)	Not reported	Not reported	Not reported
THEMIS, 2019 [12]	19,220	66	6,031 (31.4)	Not reported	Not reported	Not reported
ASPREE, 2020 [10]	19,114	74	10,782 (56.4)	Modified MMSE[d]	93.4 (4.7)	93.5 (4.6)
ASCEND, 2022 [11]	15,427	63.2	5,777 (37.4)	Not reported	Not reported	Not reported
TIPS-3, 2023 (23)	2,361	70.1	1,417 (60)	MOCA[e]	22.61 (4.92)	22.62 (4.63)

Abbreviations: SD, Standard deviation; [a]Telephone Interview for Cognitive Status (TICS) assesses global cognitive function and can be administered via telephone interview or face to face. Trials that used TICS defined a significant change in cognitive function as a reduction by greater than or equal to 4. [b]Mill Hill vocabulary scale score is a test assessing verbal reasoning, and was used in this trial to test for any large disparity between the intervention and control groups at randomisation. [c]Cognitive Abilities Screening Instrument (CASI) z score assesses global cognitive function by reporting standard deviation above or below population means. In trials that used CASI z scores, a mean score of −0.6 denoted normal cognitive function. [d]3MS (Modified Mini-Mental State Examination) assesses global cognitive function, and is derived from the Mini-Mental State Examination. Trials which used the 3MS defined 'dementia triggers' as a score <78 or a drop of more than 10.15 from predicted score based on baseline 3MS and adjustment for age and education. [e]Montreal Cognitive Assessment is a common cognitive assessment tool, testing multiple domains

Risk of bias

Risk of bias was assessed for all included trials (Supplementary Figures S2 and S3). The overall risk of bias was categorised as low in four trials [10, 11, 17, 19], and high in seven trials [12–16, 18, 20]. The majority of included trials ($n = 10$) were double-blind, randomised clinical trials, while one was open label [20]. All included trials had robust randomisation designs and adequately concealed allocation. Detection bias was identified in four trials and reporting bias was identified in five trials where adverse event reporting of evident cognitive impairment or dementia was used to report outcomes. Individual assessments of each outcome from RoB2 are provided in Supplementary Table S2.

Antiplatelet therapy and cognitive impairment or dementia

A total of 11 trials reported rates of incident cognitive impairment or dementia (109,860 participants) [10–20]. Cognitive impairment or dementia was diagnosed in 2,040 participants in the intervention group and 2,151 participants in the control group on follow-up. Antiplatelet therapy was not significantly associated with a reduction in cognitive impairment or dementia (3.49% versus 4.18% over a mean trial follow-up of 5.8 years; OR, 0.94 [95% CI, 0.88–1.00]; ARR, 0.2% [95% CI, 0.4%- -0.009%]), $I^2 = 0.0\%$) (Figure 1). Sensitivity analyses divided trials by single or dual antiplatelet treatment (P-interaction 0.53), source of data (P-interaction 0.49), risk of bias (P-interaction 0.49) or if the trial targeted primary or secondary prevention (P-interaction 0.26) did not reveal a significant difference between subgroups (Figure 2). Similarly, there was also no significant difference based on proportion of population with diabetes (P-interaction 0.50), median age (P-interaction 0.44), proportion of female participants (P-interaction 0.46) or if the trial follow-up was shorter than, or greater than or equal to 60 months (P-interaction 0.76) (Figure 2).

Antiplatelet therapy and change in cognitive score

Five trials reported on change in cognitive score [10, 11, 16, 18, 19]. Four trials [10, 11, 16, 18] (43,586 participants) used global composite scores, represented as Z scores, which were used in the meta-analysis. One study [19] reported change in individual cognitive scores without a composite Z score that could not be included in the meta-analysis. One trial (18) reported a general cognitive factor score that could not be included in the meta-analysis. Antiplatelet therapy compared with control was not significantly associated with a difference in the standardised mean cognitive score (standardised mean difference, −0.04 [95% CI, −0.04 to 0.01]; *P* value for heterogeneity = 0.18; $I^2 = 23.1\%$; Q = 4.90) (Figure 3).

Antiplatelet therapy and change in MMSE

Three trials reported change in MMSE (or a cognitive score which could be converted to MMSE) (27,536 participants). Antiplatelet therapy compared with control was not significantly associated with a difference in MMSE score (standardised mean difference, 0.00 [95% CI, −0.01 to 0.00] *P* value for heterogeneity = 0.00; $I^2 = 92.6\%$; Q = 27.14) (Figure 3).

Discussion

This meta-analysis, which included 11 trials with 109,860 participants for the primary outcome analysis with mean

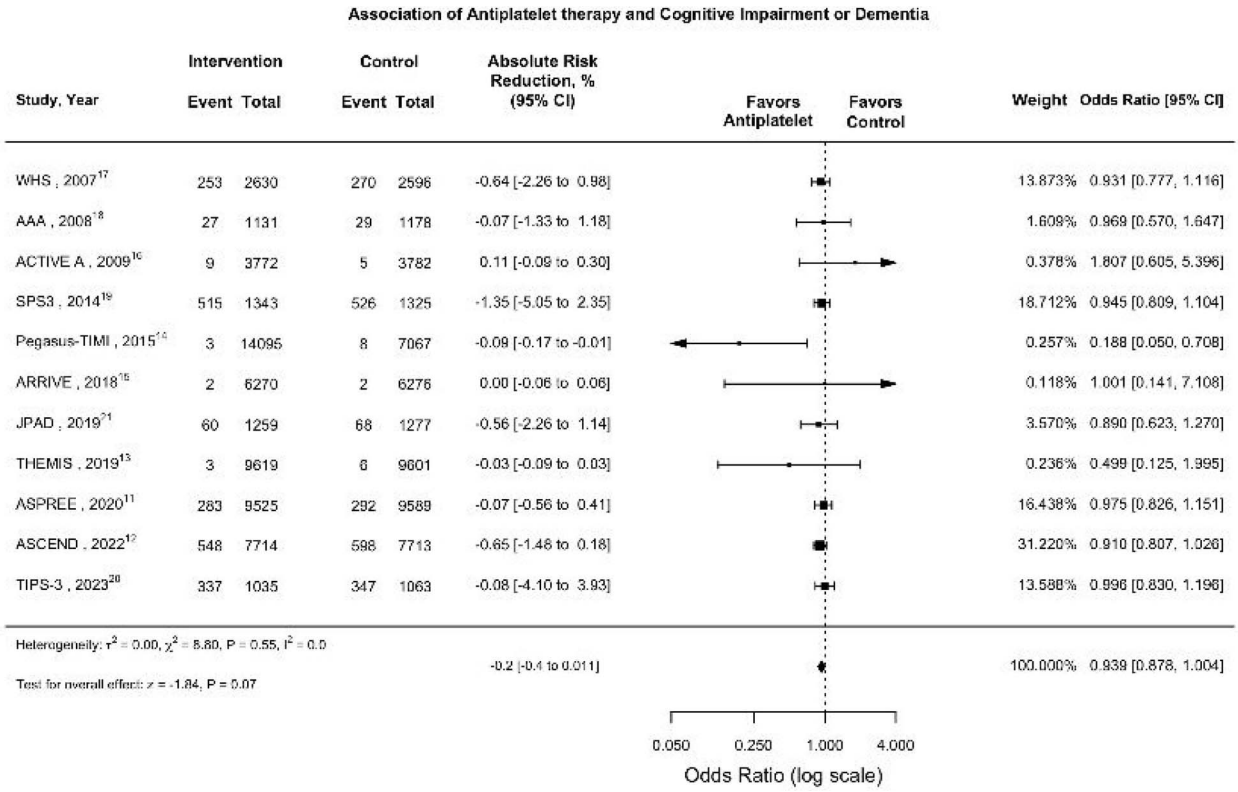

Figure 1. Association of antiplatelet therapy with incident cognitive impairment or dementia. Figure 1. Forest plot showing the effect of antiplatelet therapy effect on the incident rates of cognitive impairment or dementia. The squares and bars represent the mean values and 95% CIs of the effect sizes, and the area of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no effect.

follow-up of 5.8 years, found that antiplatelet therapy compared with control was not significantly associated with a lower risk of cognitive impairment or dementia. The CIs for this outcome do not preclude a modest treatment benefit (up to 12% risk reduction) but do essentially exclude a meaningful increase in risk (95% CI, 0.88–1.00). Low heterogeneity (I^2 = 0.0%) was observed for the primary outcome of cognitive impairment or dementia, while the low to moderate heterogeneity observed in the secondary outcomes of mean cognitive score change (Figure 3) likely reflect the differing outcome definitions and cognitive tests scores used. As outlined in Table 2, trial populations differed between included studies; however subgroup analyses (by age, sex, cardiovascular disease history) did not materially alter results. Our study provides an updated clinical trial meta-analysis of the association of antiplatelet therapy with cognitive impairment or dementia. We aimed to optimise our ability to detect an association by including all relevant clinical trials, as we suspected a modest treatment effect, if one was evident. In comparison with prior systematic reviews [11, 26, 27], we included trials investigating the effect of both single and dual antiplatelet therapy, involving a wide range of antiplatelets and included criteria based on clinically evident dementia diagnoses. We also included findings from the recently published TIPS-3 trial [19], which investigated the effects of aspirin on cognitive and functional outcomes. Compared with the most recent meta-analysis [11], we included eight additional trials with 72,783 additional participants.

While we did not report a significant reduction in the risk of cognitive impairment or dementia, our estimate is more precise than previous meta-analyses [11, 27], and suggests there may be a modest risk reduction over 5.8 years follow-up. We believe that our study, in combination with findings from recent publications such as LACI-2 [28], supports the argument that existing medications used in cardiovascular secondary prevention do not have an adverse effect on cognition, and suggests that in particular patient population these may have a beneficial effect in preventing cognitive impairment, but the latter contention requires large randomised controlled trials in specific populations (e.g. those with prior lacunar ischaemic stroke). Moreover, the reported upper limit of the CI (1.0) excludes an adverse effect on future risk of dementia. If a true effect of antiplatelet therapy does exist, it is expected to be modest (in the order of 12% relative risk or less, approximately 2 per 1,000 over 5 years), and of a magnitude that would require a very large sample size to demonstrate a significant reduction in dementia in a primary prevention population. Against this, in a primary prevention population, aspirin is associated with a 29% relative increase in intracerebral haemorrhage [29], with a

Table 2. Characteristics of included studies in the analysis of antiplatelet therapy and incident cognitive impairment or dementia

Trial	Intervention primary outcome event/total (%)	Control primary outcome event/total (%)	Trial design	Study population	Prevention population	Intervention group	Control group	F/U months	Primary outcome	Dementia or cognitive impairment criteria	Cognitive score used
WHS, 2007 [16]	253/3215 (7.87%)	270/3162 (8.53%)	Randomised, double blind, placebo control	Women, age > 65, no prior cardiovascular disease	Primary	Aspirin 100 mg	Placebo	115	Global cognitive score	Lowest 10% of the distribution of cognitive scores from the initial to the final cognitive assessment	Global cognitive score[a], TICS[b]
AAA, 2008 [17]	27/1131 (2.39%)	29/1178 (2.46%)	Randomised, double blind, placebo control	Age 50–75, no prior cardiovascular disease	Primary	Aspirin 100 mg	Placebo	57	Composite cognitive score	MMSE[c] score < 24	MMSE[c]
ACTIVE A, 2009 [15]	9/3772 (0.24%)	5/3782 (0.13%)	Randomised, double blind, placebo control	Diagnosis of atrial fibrillation and one additional risk factor for stroke	Primary	Aspirin 75-100 mg plus Clopidogrel 75 mg	Aspirin 75-100 mg plus placebo	43	Stroke, myocardial infarction or vascular death	Clinically evident	None reported
SPS3, 2014 [18]	515/1343 (38.35%)	526/1325 (39.70%)	Randomised, double blind, placebo control	Age > 30, lacunar stroke within previous 6 months	Secondary	Aspirin 325 mg plus Clopidogrel 75 mg	Aspirin 325 mg plus placebo	60	CASI[d] Z score	CASI[d] Z score of 1.5 SD below the mean	CASI z score[d]
PEGASUS-TIMI, 2015 [13]	3/14095 (0.02%)	8/7067 (0.11%)	Randomised, double blind, placebo control	Age > 50, history of ischaemic heart disease	Secondary	Aspirin 75-150 mg plus Ticagrelor 90 mg or 60 mg	Aspirin 75-150 mg plus placebo	33	Stroke, myocardial infarction or vascular death	Clinically evident	None reported
ARRIVE, 2018 [14]	2/6270 (0.03%)	2/6276 (0.03%)	Randomised, double blind, placebo control	Males >55, Females >60, high risk for cardiovascular disease	Primary	Aspirin 100 mg	Placebo	60	Stroke, myocardial infarction or vascular death	Clinically evident	None reported
JPAD. 2019 [20]	60/1259 (4.77%)	68/1277 (5.32%)	Randomised, open-label	Age 30–85, diagnosis of type two diabetes	Primary	Aspirin 81-100 mg	Standard care	136	Prescription of antidementia drugs or long term care admission due to dementia.	Prescription of antidementia drugs or long term care admission due to dementia.	None reported
THEMIS, 2019 [12]	3/9619 (0.03%)	6/9601 (0.06%)	Randomised, double blind, placebo control	Age > 50, stable coronary artery disease and type two diabetes	Secondary	Aspirin 75-150 mg plus Ticagrelor 60 mg	Aspirin 75-150 mg plus placebo	40	Stroke, myocardial infarction or vascular death	Clinically evident	None reported
ASPREE, 2020 [10]	283/9525 (2.97%)	292/9589 (3.05%)	Randomised, double blind, placebo control	Age > 65, no prior cardiovascular disease	Primary	Aspirin 100 mg	Placebo	56	Incident dementia	DSM-IV criteria	3MS[e], Composite cognitive score[f]
ASCEND, 2022 [11]	548/7714 (7.10%)	598/7713 (7.75%)	Randomised, double blind, placebo control	Age > 40, diagnosis of type two diabetes, no prior cardiovascular disease	Primary	Aspirin 100 mg	Placebo	110	Incident dementia	ICD-10 criteria, prescription of dementia medication, referral to memory clinic	Global cognitive score[g]
TIPS-3, 2023	337/1160 (29.05%)	347/1201 (28.89%)	Randomised, double blind, placebo control	Age > 65, with no prior cardiovascular disease, but at intermediate cardiovascular risk	Primary	Aspirin 75 mg	Placebo	60	Composite outcome of cognitive scores	1.5 standard deviation decline at final assessment from the baseline country standardised scores	Composite cognitive outcome[gh]

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases. [a]Global cognitive score in this trial averaged performances across five cognitive tests (TICS, immediate and delayed recalls of east Boston memory test, delayed recall of 10-word list, and category fluency), using z scores. [b]Telephone Interview for Cognitive Status (TICS) assesses global cognitive function and can be administered via telephone interview or face to face. Trials that used TICS defined a significant change in cognitive function as a reduction by greater than or equal to 4. [c]Mini-Mental State Examination (MMSE) assesses global cognitive function. Scores range from 0 to 30, with higher scores indicating better cognitive function; a score greater than 26 represents normal cognitive function. For trials that reported MMSE score, a score of less than 24 was used as a 'screen' for cognitive impairment. [d]Cognitive Abilities Screening Instrument (CASI) z score assesses global cognitive function by reporting standard deviation above or below population means. In trials that used CASI z scores, a mean score of −0.6 denoted normal cognitive function. [e]3MS (Modified Mini-Mental State Examination) assesses global cognitive function and is derived from the Mini-Mental State Examination. Trials which used the 3MS defined 'dementia triggers' as a score <78 or a drop of more than 10.15 from predicted score based on baseline 3MS and adjustment for age and education. [f]Composite cognitive score is a global composite cognitive score, an average of the cognitive tests 3MS, HVLT-R Delayed Recall, COWAT and SDMT using z scores of each test. Scores for each test were standardised into z scores based on mean and SD of the test at baseline. [g]Global composite cognitive score is a cognitive function z-score, comprising modified Telephone Interview for Cognitive Status, Verbal Fluency and Healthy Minds cognitive tests, with cognitive z-score difference is adjusted for age at test and sex, and the effect of aspirin allocation estimated using linear regression. [h]Composite cognitive outcome is a combination composite score comprised of Montreal Cognitive Assessment, Digital Symbol Substitution Test, Trail Making Test-B, Standard Assessment of Global Everyday Activities cognitive test

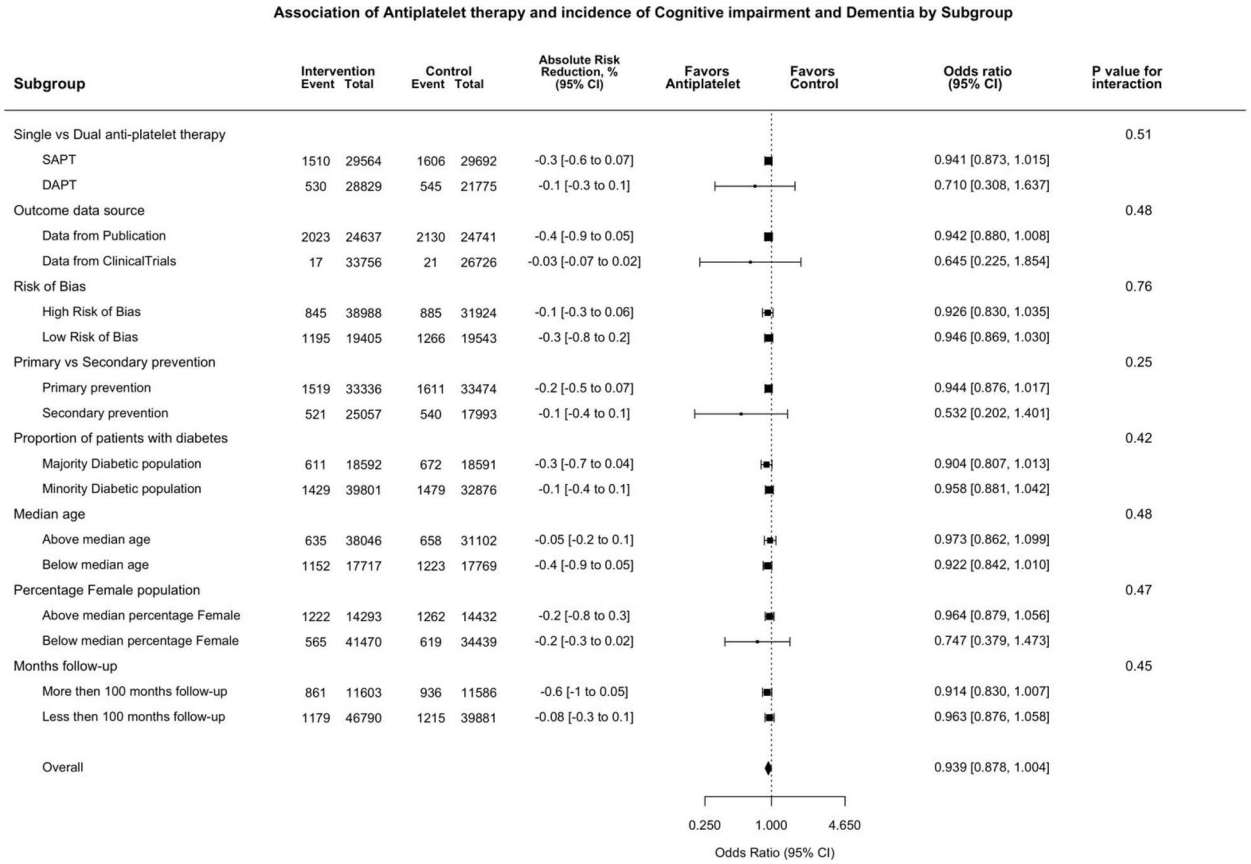

Figure 2. Association of antiplatelet therapy with incidence of cognitive impairment or dementia by subgroup. Figure 2. Forest plot showing the association of antiplatelet therapy with incident cognitive impairment or dementia, by subgroup. The squares and bars represent the mean values and 95% CIs of the effect sizes, and the area of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no effect.

reported number needed to harm (NNH) of about 500. Applying the point-estimate reduction in risk of cognitive impairment/dementia associated with antiplatelet therapy reported in our analysis, the number needed to treat (NNT) to prevent one case of mild cognitive impairment or dementia was 413 (95% CI, 206 to −6,330), meaning a net neutral effect from these two neurovascular clinical outcomes. The recently updated guidelines from the USPSTF in 2022 does not recommend aspirin use in primary prevention of cardiovascular disease in those over the age of 60 years [30], and a Cochrane review from 2020 found that there is no clear evidence to support the use of aspirin for the prevention of dementia [26].

In general, observational studies have reported a moderate reduction in risk of dementia and cognitive decline associated with aspirin use [27, 31], and we await the long-term follow-up of clinical trials [32] evaluating antiplatelet therapy in populations with mild cognitive impairment, to determine whether they reduce the rate of cognitive decline. While the population included in our meta-analysis does not include participants with established cognitive impairment, our findings would suggest that any effect of antiplatelet therapy is expected to be small, and estimates from observational research studies are likely to reflect confounding or other bias.

Dementia and cognitive impairment were not a primary outcome of any of the clinical trials included, and therefore none were designed (or powered) to detect significant reductions in incident dementia. Moreover, the definition of dementia among trials that measured this outcome varied, supporting the need for a core outcomes set in cardiovascular prevention trials. Relatively long-term follow-up is required to assess for dementia and cognitive impairment [33], and there remains a strong possibility that insufficient treatment durations within clinical trials may be contributing to the non-significant findings reported by this meta-analysis, especially given the mean age of total participants in the review was 65.9, with an average mean follow-up of 5.8 years. Another strategy to address this research question would be linkage of individual participant data to electronic health records with information on cognitive outcomes. This has been conducted in blood pressure lowering trials allowing the long-term follow-up of large patient numbers [34]. Overlapping neuropathology frequently exists [35] in patients with cognitive impairment/dementia, and while antiplatelet therapy is expected to affect the natural history of vascular

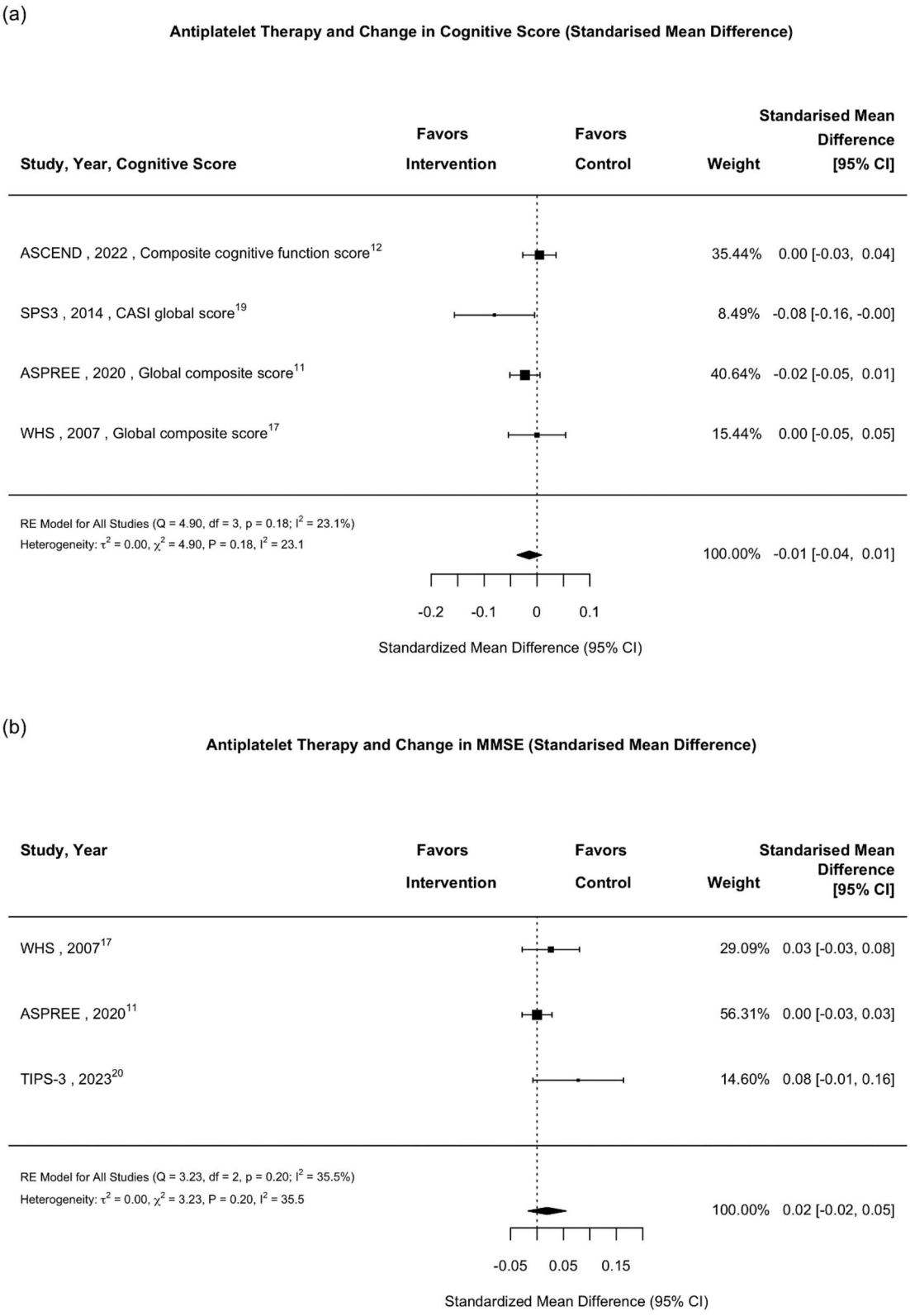

Figure 3. Association of antiplatelet therapy and mean change in cognitive scores. Figure 3. Forest plot showing the effect of antiplatelet therapy effect on the mean change in cognitive scores, in combined cognitive z-scores (a), and change in MMSE (b). The squares and bars represent the mean values and 95% CIs of the effect sizes, and the area of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no effect. RE-Random Effect

cognitive etiologies, it may have no effect on Alzheimer's type neurodegenerative process.

Measurement of cognitive outcomes presents a challenge in clinical trials, particularly with loss to follow-up occurring preferentially in populations who develop dementia. Accordingly, a future definitive trial should consider functional outcome measures which are less likely to incur missing information on follow-up. Functional decline was reported in the TIPS-3 [19] trial to be more a more sensitive outcome to the effects of polypill then cognitive outcomes. Novel approaches that highlight biomarkers such as cerebral small vessel are needed to select out populations most likely to benefit from antiplatelet agents [31], as convincing biological mechanisms exist to suggest antiplatelet agents may be associated with reductions in the incidence of vascular dementia [36]. However, systematic reviews investigating antithrombotic therapy in small vessel disease [37] have similarly found that heterogeneity in the existing literature, in population included, trial design and outcome ascertainment, greatly limits our ability to provide confidant findings.

Limitations

This study has several limitations. First, there was heterogeneity in trial designs, class of antiplatelet, study population and differing definitions of cognitive outcomes and scales used among trials. In particular, few trials systematically assessed for a criterion-defined diagnosis of dementia. However, we observed no evidence of statistical heterogeneity among trials. Second, trials that investigate dementia incidence are prone to preferential loss of follow-up of participants with dementia leading to potential under-reporting, which may have diminished any treatment effect. Third, the low incidence of dementia in all clinical trials, despite the large number of participants, reduced power to detect differences in treatment effect. Fourth, the estimate for change in MMSE is based on secondary analysis of cognitive scores (3MSE, MOCA and TICS) converted to MMSE. While validated scales were used in this conversion, the interpretation of these estimates should be approached with caution.

Conclusions

In this meta-analysis of randomised clinical trials, antiplatelet therapy was not significantly associated with a lower risk of incident cognitive impairment or dementia, but the CIs around this outcome do not exclude a modest preventative effect.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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Data Availability: The full dataset and statistical codes will be available on reasonable request from any qualified investigator.

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