

EVALUATING THE COGNITIVE BENEFITS OF DIHYDROPYRIDINE CALCIUM CHANNEL BLOCKERS IN DEMENTIA PREVENTION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background

Dementia is a major global health challenge, and antihypertensive drugs may influence its risk. This study aimed to evaluate whether dihydropyridine calcium channel blockers (DHP-CCBs) reduce the chance for having dementia compared to other antihypertensives.

Methods

We conducted a systematic search through PubMed and Google Scholar to identify eligible studies between 1989 to 2024, including randomized controlled trials, cohort, and longitudinal studies of adults without baseline dementia that compared DHP-CCBs with other antihypertensives or placebo. Risk of bias was assessed for RCTs and observational studies using the Cochrane RoB2 tool and the MINORS tool, respectively.

Results

Eleven studies were included, three of which contributed to meta-analysis. Pooled results showed no significant reduction in all-cause dementia risk with DHP-CCBs (RR = 0.89, 95% CI [0.78, 1.02], p = 0.10), with concomitant homogenous pooled studies (I^2 = 12.65%, p = 0.32). Sensitivity analysis revealed a significant reduction after excluding one study (RR = 0.89, 95% CI [0.83, 0.95], p = 0.001). Subgroup analysis demonstrated lower dementia risk with DHP-CCBs compared to ACE inhibitors and ARBs, but not against beta-blockers, non-DHPs, or diuretics.

Conclusion

Overall, DHP-CCBs were not significantly associated with reduced dementia risk. Although subgroup and sensitivity analyses suggest a potential benefit compared with ACE inhibitors and ARBs, the evidence remains limited due to the limited number of eligible studies, incomplete reporting of dosage and administration routes, and insufficient stratification by dementia subtypes. Further well-designed studies with standardized cognitive assessments are warranted to better establish their potential role in dementia prevention.

KEYWORDS: Dihydropyridine, Calcium Channal Blockers, ACEIs, Beta-blockers, ARBs, Diuretics, Non-Dihydropyridine, Dementia, Alzheimer's disease, Cognitive, Vascular dementia

INTRODUCTION

Dementia is a common neurological illness that can be predisposed by multiple factors, which with time could damage the nerve cells and the brain. Dementia is the leading cause of deterioration of cognitive function, and it interferes with daily activities. Alzheimer's disease is considered to be the most common type of dementia, which accounts for approximately 60-70% of cases. Data suggest that there are 10 million new cases diagnosed globally every year, and it is considered the seventh leading cause of death (1).

Hypertension is one of the most important modifiable risk factors of dementia. However, the relationship between hypertension and dementia is complicated and not entirely understood (2). Due to this association, efforts to investigate whether antihypertensives used to manage hypertension may reduce the risk of dementia have been conducted, but with no consistent findings (3).

Dementia's slow progression complicates research. Detecting significant outcomes often requires long-term follow-up in large populations. While observational studies are abundant, they often suffer from confounding variables, and randomized controlled trials on this topic remain limited in number and scope.

Another reason for this uncertainty is the wide range of antihypertensive drug classes—such as dihydropyridines (DHPs), beta-blockers, angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), diuretics, and others. Each type may influence the brain and blood vessels differently. Even within the same class, specific drugs can vary in their effects, making direct comparisons difficult and findings inconsistent.

Researchers have invested substantial effort into understanding how these medications influence the likelihood of dementia. Some studies proposed that calcium channel blockers (CCBs) show a protective benefit in reducing the chance of having dementia when compared to other classes of antihypertensive medications (4–7). This suggests that patients treated with CCBs may experience a lower likelihood of cognitive decline relative to those receiving different types of blood pressure-lowering drugs (4). Other studies supported such statement by providing Evidence which strengthens the idea that initiating antihypertensive therapy especially with a long-acting dihydropyridine helps protect against dementia (8). However, others show minimal impact, with findings suggesting little to no effect on the development of dementia in individuals treated with these medications. A significantly greater proportion of individuals taking calcium channel blockers (CCBs) experienced a decline in cognitive performance over the study period compared to those using other antihypertensive medications (9). As a result, the conclusions remain mixed, with some research supporting the potential benefits while others remain skeptical, underscoring the complexity of the association between hypertension treatments and brain health.

Our study stands out in this area of research due to several major strengths, including a large sample of 300,972 patients drawn from 11 studies across North America, Europe, and Asia, which can enhance the robustness of the findings. This systematic review compares DHPs with several other antihypertensive classes, such as beta-blockers, ACEIs, ARBs, diuretics, and non-DHPs, offering a comprehensive perspective. By examining associations between DHP-CCBs use and cognitive outcomes, we believe this review may provide valuable insight for clinical decision-making, potentially identifying treatments that offer both cardiovascular and cognitive protection.

METHODS AND MATERIALS

Ethics and Registration

This systematic review is registered on the international systematic review registry (PROSPERO; CRD42024603008) and carefully followed the preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.

Literature Search and Search strategy

This study was carried out as a comprehensive literature review to evaluate the cognitive benefit of dihydropyridine calcium channel blockers in dementia prevention using PubMed and Google Scholar to identify pertinent studies within the period between 1989 to 2024. The search strategy employed the following keywords: terms related to cognitive impairment (cognitive decline, dementia, vascular dementia, or Alzheimer's disease); terms related to calcium channel blockers class (dihydropyridines, nitrendipine, nicardipine, cilnidipine, lercanidipine, nimodipine, azelnidipine, nilvadipine); and terms related to the cognitive outcomes (cognitive function, dementia incidence, memory decline, or neurodegenerative disorders).

Eligibility criteria

Research selection was carried out independently by three authors who screened the titles and abstracts of potential studies. Next, eight authors screened the full manuscripts independently to extract studies that meet the inclusion criteria: (1) studies that included adults aged 18 years or older, free from cognitive decline or dementia at baseline; (2) studies that involve specific dihydropyridine calcium channel blockers (e.g. nitrendipine, nicardipine, cilnidipine, lercanidipine, nimodipine, azelnidipine, nilvadipine) for cognitive protection; (3) studies in which the comparator groups included patients receiving other antihypertensive agents, placebos, or no treatment; (4) studies with the primary outcomes including cognitive function decline, incident dementia, Alzheimer's disease, or vascular dementia; (5) studies that are RCTs, cohort studies, or observational longitudinal studies which analyze cognitive outcomes. We excluded studies meeting the following criteria: (1) studies that included patients with pre-existing cognitive impairment, dementia, or severe comorbid conditions (e.g. cancer, HIV, etc.); (2) studies investigating the effect of non-specific calcium channel blockers (e.g. non-dihydropyridines); (3) studies without a comparison group, or studies that only focus on postoperative cognitive outcomes; (4) studies that do not report on cognitive function or dementia-related outcomes; (5) case reports, narrative reviews, animal studies, conference abstracts, and non-peer-reviewed articles.

Selection and screening

Initially, our search strategy resulted in a total of 349 studies, which were uploaded to Rayyan AI software for title and abstract screening by three reviewers. Eleven studies were eventually included after careful full text screening that was carried out by all the eight authors. Reasons for exclusion of studies in the full text screening stage are further elaborated in **Figure 1**.

Data extraction

Data extraction was performed by eight authors for the following variables: year of publication, country of origin, study design, sample size (extracted as follows: the number of patients involved in each group [Group 1: dihydropyridine CCBs, Group 2: other CCBs, Group 3: non-CCBs], in addition to the total number), patient demographics (age, sex, mean blood pressure, mean body mass index, comorbidities), primary and secondary outcomes including the number of patients developing dementia after treatment.

Risk of bias assessment

The included studies were assessed for quality and bias using the Cochrane Risk of Bias (RoB2) tool for randomized trials and the Methodological Index for Non-randomized Studies (MINORS) tool for observational cohort studies. A total of five studies were evaluated using the RoB2 tool, and seven studies were assessed using the MINORS tool. The RoB2 tool evaluates bias across five domains; the risk of bias is determined as high risk, some concerns, or low risk within each domain. The MINORS tool comprises 12 items, with each item scored on a scale from 0 to 2, where 0 indicates non-reporting, 1 indicates inadequate reporting, and 2 indicates adequate reporting. Eight authors independently assessed each study and resolved any disagreements through discussion until reaching a consensus.

Statistical analysis

The event and total were extracted for the dichotomous data and pooled through a Der Somnian Laird random effect model as risk ratio (RR) and 95% Confidence interval (CI). The statistical significance was deemed when the p-value reached < 0.05 . The significant heterogeneity was identified when the chi-square p-value reached < 0.1 or $I^2 > 50\%$. The leave-one-out test was done to ensure the reliability and robustness of pooled estimates, in which one study was omitted in each scenario to confirm that no single study has a determinantal impact on the pooled estimate. We executed a subgroup analysis according to the type of antihypertensive medication used in the control group. All the statistical analysis was executed utilizing STATA BE 18.5.

RESULTS

Characteristics of the included studies

Eleven studies (4–6,8,10–16), comprising 300,972 patients, were included in this systematic review, of which four were RCTs and seven were observational studies. The included studies were conducted in multiple geographical areas, with six studies conducted in North America, three in Europe, and two in Asia. The mean age of this study population was 69 years, ranging from 56.8 years to 79 years. In-depth information regarding the characteristics of the included studies is presented in **Table 1**.

Risk of bias

Four RCTs were evaluated using ROB2, all of which were classified as having some concerns, as presented in **Table 2**. The Minors tool was used to assess the risk of bias in the observational studies, with a score ranging from 13 to 21. Detailed information regarding the risk of bias in all of the included studies is presented in **Table 3**.

Dementia

Three studies reported dementia rates, incorporating 12,520 patients in the DHP-CCBs group and 10,399 patients in other AHMs group. The pooled analysis did not reveal any significant difference between the two groups in terms of all-cause dementia risk (RR = 0.89, 95% CI [0.78, 1.02], $p = 0.10$), with concomitant homogenous pooled studies ($I^2 = 12.65\%$, $p = 0.32$), as illustrated in **Figure 2**.

The leave-one-out test was done to ensure the robustness of the results. It demonstrated a significantly lower dementia risk with DHPs upon omitting Khachaturian et al. (RR = 0.89, 95% CI [0.83, 0.95], $p = 0.001$), as displayed in **Figure 3**.

To investigate the source of heterogeneity, a Galbraith plot was constructed, which exhibited a homogeneous pattern with the three studies located within the 95% CI precision area of the regression line, as outlined in **Figure 4**.

The subgroup analysis based on the type of other AHMs demonstrated a significantly lower dementia risk with DHPs compared to ACEIs (RR = 0.79, 95% CI [0.75, 0.84], $p = 0.001$) or ARBs (RR = 0.77, 95% CI [0.74, 0.80], $p = 0.001$), as outlined in **Figure 5**. Nevertheless, we did not find any substantial differences between the DHPs and BBs (RR = 0.88, 95% CI [0.60, 1.29], $p = 0.50$), non-DHPs (RR = 1.82, 95% CI [0.46, 7.29], $p = 0.40$), or diuretics (RR = 0.81, 95% CI [0.63, 1.05], $p = 0.12$), as illustrated in **Figure 5**.

DISCUSSION

We conducted this systematic review to examine the role of DHP CCBs in dementia prevention and on cognitive function. Eleven studies were included with a total of 300,972 participants, and only 3 were incorporated into the current meta-analysis. In patients without dementia at baseline, the use of DHP-CCBs does not appear to be significantly associated with decreased all-cause dementia risk. However, upon conducting a sensitivity analysis using leave-one-out test, we found that the exclusion of one study resulted in a statistically significant difference. In addition, sub-group analysis revealed a significant reduction in dementia risk with DHP CCBs compared to ACEI and ARBs, but no considerable difference when compared to BBs, non-DHPs or diuretics.

Hypertension has been considered a modifiable risk factor for dementia and other cerebrovascular lesions (2). It was assumed that blood pressure control using AHMs could affect the cognitive function and perhaps decrease the incidence of dementia (17,18). Several papers have studied the effect of different AHMs classes on cognitive function and the preventing dementia (3,18,19) with no common agreement on which class is more effective. One such study was the Systolic Hypertension in Europe (Syst-Eur) trial, which evaluated the use of a specific DHP calcium channel blocker, nitrendipine, with possible add-on therapy of enalapril and hydrochlorothiazide, for managing isolated systolic hypertension in elderly patients (9,11,20). It was shown that initial treatment with nitrendipine decreased the rate of dementia rate by 55% (11). Likewise, other studies showed the positive effect of CCBs on cognitive function (7) especially DHPs as nimodipine (21) and nilvadipine (22). However, there are

some inconsistencies in literature when it comes to the certainty of these results. Data from The Baltimore Longitudinal Study of Aging were used to explore the association between CCBs use and the development of Alzheimer's disease (AD) (4). In particular, the aim of the study was directed toward whether those beneficial effects were related to the use of DHP or non-DHP-CCBs. Results showed that the use of CCBs had no significant difference in the risk of AD development. Even though there was an observed trend for decreasing AD development with DHP-CCBs, the authors proposed that the failure to demonstrate a significant reduce in the incidence of AD with DHP-CCBs might be due to the high variability of patients using this type at the time of the study period and their limited number. A large study in the Netherlands found a significance risk reduction for CCBs (HR = 0.77; 95% CI = 0.71–0.84) but with no differences within the CCB subclasses (19). Another multinational population study comparing different classes of AHMs concluded that the initiation of ARBs is linked to a lower risk of dementia compared to ACEIs, but no statistically significant association with the other classes including CCBs (3). Data from the Cache County Study (8) showed a significant risk reduction with potassium sparing diuretics, and no significant reduction with CCBs or ACEi. The last two mentioned studies did not report on the differences between CCBs subclasses. As discussed, it appears that the evidence investigating the role of DHP CCBs specifically in preventing dementia is still lacking to be inclusive, and this uncertainty is still apparent in our meta-analysis. To date, there are no recommendations regarding the use of this class in preventing dementia or similar diseases. To date, no clinical practice guidelines recommend the use of DHP CCBs for the prevention of dementia, and only nimodipine has been recommended for patients with aneurysmal sub-arachnoid hemorrhage (aSAH) to prevent delayed cerebral ischemia and improving functional outcomes (23,24)

Strengths, Limitations and Future Recommendations

This systematic review has several strengths: data extraction was done by all authors, and the extraction process was reviewed and repeated multiple times to ensure comprehensiveness, accuracy and preciseness. Furthermore, this review integrated a large number of patients from different geographical areas, increasing generalizability of the results. Nevertheless, there are some limitations that should be considered: limited reporting on the dose and route of administration, the specific sub-type of dementia prevented, and the concerning risk of bias of the studies included could negatively impact the overall outcome. Future RCTs and head-to-head comparisons thoroughly exploring the effect of DHP-CCBs on dementia prevention are strongly encouraged to fill in the gap within the currently available evidence, and further help establish a clear insight on the extent to which these agents and different others can mitigate the risk of dementia by managing the predisposing factors, facilitating the advancement in dementia and aging field.

CONCLUSION

Dihydropyridine calcium-channel blockers (DHP-CCBs) are not associated with a significant reduction in all-cause dementia risk in the primary pooled analysis. A leave-one-out sensitivity analysis indicated a significant association after excluding one study, while subgroup analyses suggested a lower dementia risk compared to ACEIs and ARBs, but not versus beta-blockers, non-DHPs, or diuretics.

The certainty of the evidence is limited by the limited number of studies contributing to the pooled estimate with some risk-of-bias concerns, incomplete reporting of dosage and administration routes, and limited stratification by dementia subtype. Based on the insights provided by the current analysis, clarifying the cognitive impact of DHP-CCBs in dementia prevention will require well-designed studies with standardized cognitive outcomes and rigorous confounding control. If future evidence confirms a benefit, these agents could become a targeted therapeutic option; however, more robust data are needed before clinical adoption. These considerations should inform both the design of upcoming trials and the interpretation of future evidence within this domain.

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Table 1: Characteristics of the included studies.

first author and year	country	Study design	sample size			Total
			Group 1 (dihydropyridine group)	Group 2 (non-dihydropyridine group)	Group 3 (non-CCB group)	
Hwan. 2016	South Korea	Cohort study	11,816	269	4,731	18,423
S. Yasar, 2005	United State	prospective study	78	104	80%	1092
Francoise Forette, 2002	United State	RCT	1485	NR	1417	2902
Ruth Peters, 2015	UK	cohort	32	32	159	238
Maxwell CJ, 1999	Calgary	prospective	23	45	B-blocker : 37 - ACE inhibitor : 34 - Thiazide diuretic:56 - other:10	205
Colbourne L and Harrison PJ, 2022*	UK	Cohort	44,731 (Brain penetrating CCBs)	44,731 (Amlodipine)	NR	89462
Colbourne L and Harrison PJ, 2022*	UK	Cohort	49,987 (Brain penetrating CCBs)	49,987 (Verapamil or Diltiazem)	NR	99974
Colbourne L and Harrison PJ, 2022*	UK	Cohort	38,305 (Brain penetrating CCBs)	38,305 (ARBs)	NR	76610
T Ogihara , 2000	Japan	randomized, double-blind comparative trial	176	NR	160	336
van Middelaar, Tessa , 2017	The Netherlands	Randomized Controlled Trial (subgroup analysis from preDIVA trial)	395	127	1429	1951
Ara S. Khachaturian, 2006	United States	Population-based prospective cohort	192	288	2737	3217
Michael H. Skinner, 1992	California, USA	Randomized, double-blind, crossover trial	11	NR	14	25
Phillip J. Tully, 2016	America	Cohort	4.8%	3%	ACEI (10.4%), ARB (5.9%), potassium-sparing diuretic (5.6%), loop diuretic (2.3%). a-receptor blocker (2.2%). thiazide	6537

					diuretic (1.1%)	
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* This study compared the effects of Brain-penetrating CCBs to 3 different comparators in 3 cohorts; therefore, we considered each of the cohorts as a separate group.

ARBs: Angiotensin Receptor Antagonists.

Table 2: Risk of bias assessment by ROB2 for RCTs studies

Item	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall ROB2
Francoise Forette, 2002	Some concerns	low	Low	Low	Some concerns	Some concerns
T Ogihara , 2000	Some concerns	Low	Low	Some concerns	Low	Some concerns
van Middelaar, Tessa, 2017	Low	Low	Low	Low	Some concerns	Some concerns
Michael H. Skinner, 1992	Some concerns	Low	Some concerns	Low	Low	Some concerns

Table 3: Risk of bias assessment by Minors tool for cohort studies

Item	Hwan. 2016	S. Yasar, 2005	Ruth Peters, 2015	Colleen J, 1999	Colbourne L and Harrison PJ, 2022	Ara Khachaturian, S. 2006	Phillip J. Tully, 2016
A clearly stated aim	2	2	2	1	2	2	2
Inclusion of consecutive patients	2	0	2	2	1	2	2
Prospective collection of data	2	2	2	2	0	2	2
Endpoints appropriate to the aim of the study	2	2	1	1	2	2	2
Unbiased assessment of the study endpoint	0	0	2	2	1	2	1
Follow-up period appropriate to the aim of the study	2	2	2	2	2	2	2
Loss to follow up less than 5%	0	0	2	1	1	0	2
Prospective calculation of the study size	0	0	2	1	0	0	0
Additional Items							
An adequate control group	2	2	0	2	2	2	2
Contemporary groups	2	1	2	0	2	2	2
Baseline equivalence of groups	2	0	2	0	1	1	1
Adequate statistical analyses	2	2	2	0	2	2	2

Total score	18	13	21	14	16	19	20
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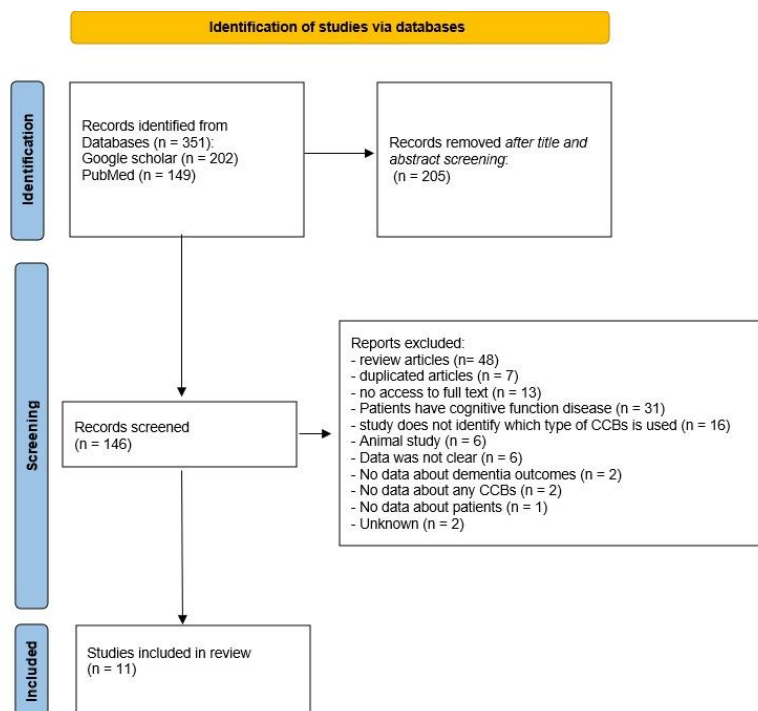


Figure 1: Prisma flowchart diagram for the systematic review

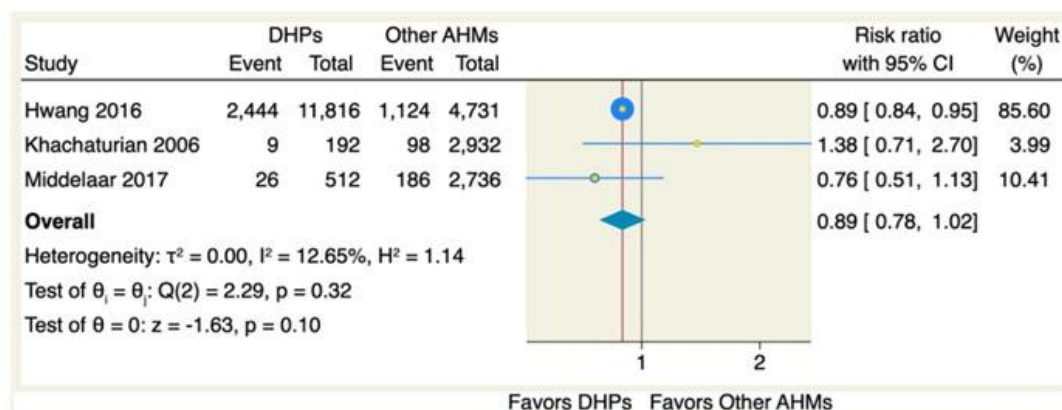


Figure 2: Forest plot of dementia.

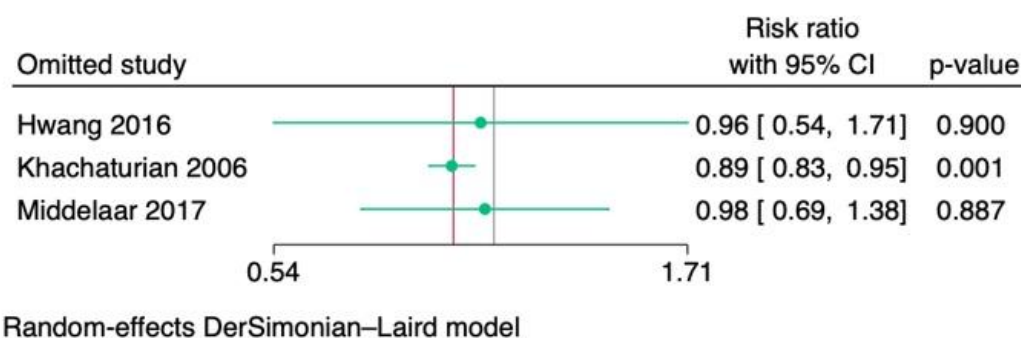


Figure 3: Leave-one-out plot of dementia.

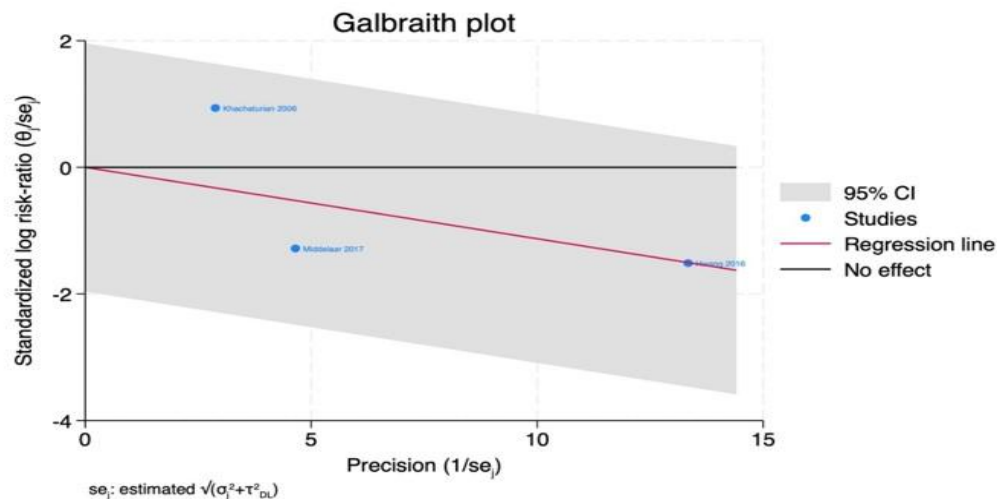


Figure 4: Galbraith plot for dementia.

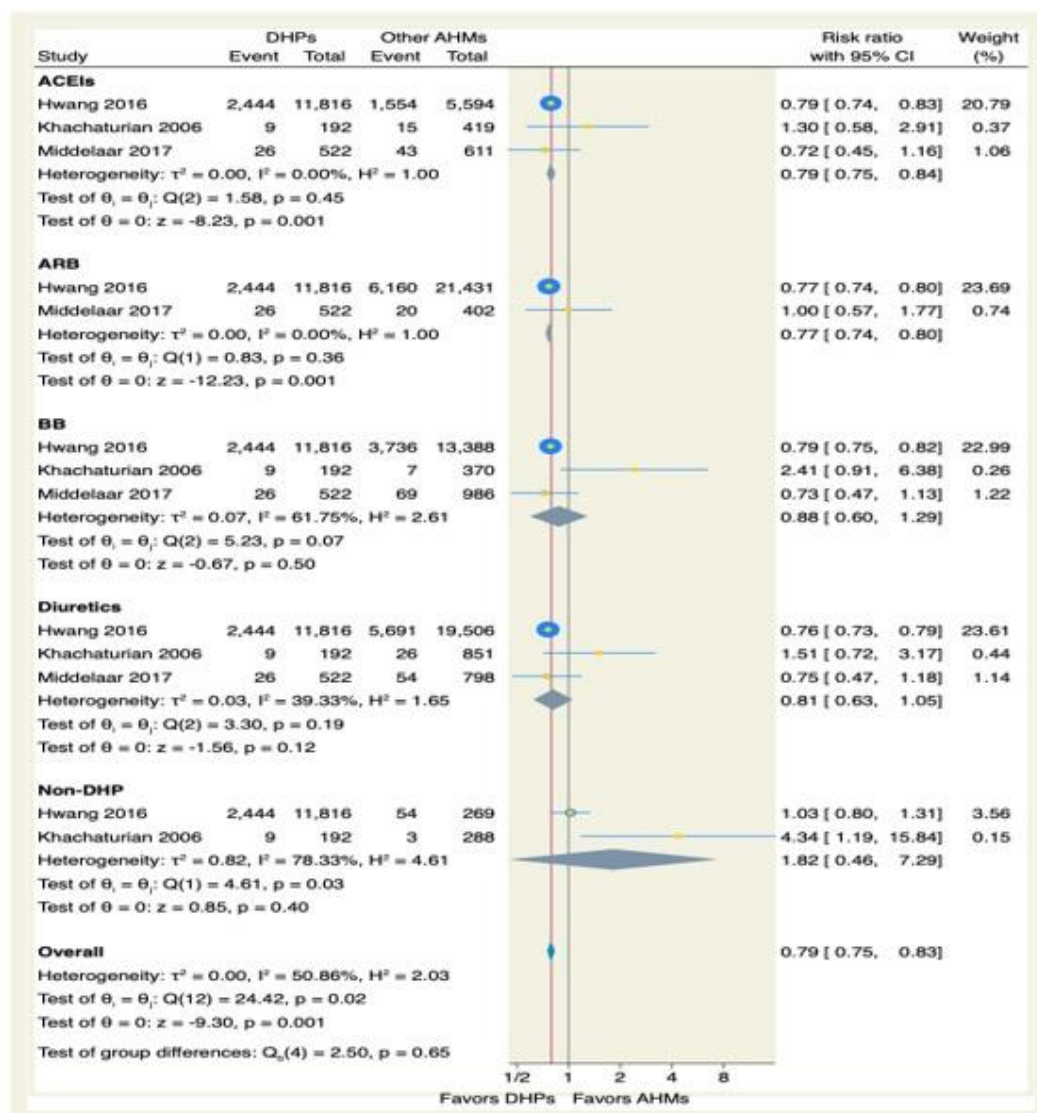


Figure 5: Forest plot of subgroup analysis according to comparator type.