

BACE1 Inhibitors versus Placebo in the Treatment of Alzheimer's Disease: A Meta-Analysis

Harish Sidharth Veerachamy^{1*‡}, Jacintha Jayavani Jayakaran^{2‡}, Gurunathan Srinivasan², Praveen Nandha Kumar Pitchan Velammal³

¹ Barking, Havering and Redbridge University Hospitals NHS Trust (BHRUT), UK ² Stanley Medical College, Chennai, India ³ University of Tennessee Health Science Center (UTHSC), Memphis, USA ^{*} Presenting Author [‡] Joint First Authors

BACKGROUND

BACE1 (β-site amyloid precursor protein–cleaving enzyme 1) is the rate-limiting enzyme in the production of amyloid-β (Aβ), whose accumulation into plaques is a defining feature of Alzheimer's disease.

Under the amyloid hypothesis, inhibiting BACE1 should lower Aβ generation and slow disease progression, making it an attractive drug target. Yet individual randomised trials have raised concerns about both the efficacy and the safety of these agents.

This meta-analysis pools the available randomised evidence to compare the efficacy and safety of BACE1 inhibitors versus placebo in Alzheimer's disease.

METHODS

A systematic review and meta-analysis was conducted and reported in accordance with the PRISMA guidelines.

Major electronic databases were searched **up to January 2026** for randomised controlled trials comparing BACE1 inhibitors with placebo in patients with Alzheimer's disease or prodromal AD.

Efficacy was assessed with cognitive/functional scales (CDR-SB, MMSE, ADAS-Cog-11) and safety with treatment-emergent adverse events (TEAEs). Continuous outcomes were pooled as **mean differences (MDs)** and dichotomous outcomes as **risk ratios (RRs)**, using fixed- or random-effects models with heterogeneity quantified by the I² statistic.

KEY FINDINGS

7

Randomised studies included

9,206

Patients with Alzheimer's disease

0

Outcomes favouring BACE1 inhibitors

9

Adverse-event signals significantly increased

CONCLUSION

No cognitive benefit. BACE1 inhibitors showed no significant advantage over placebo in slowing dementia progression, and on the CDR-SB they were associated with slightly worse cognition.

Broad harm. They were consistently linked to a substantially wider adverse-event profile — spanning hepatic, neuropsychiatric, dermatological and gastrointestinal events.

Taken together, current randomised evidence does not support BACE1 inhibitors as a suitable treatment option for Alzheimer's disease, though further well-designed RCTs are needed before a definitive conclusion can be drawn.

RESULTS

Seven randomised controlled trials, together enrolling **9,206 patients** with Alzheimer's disease, met the inclusion criteria.

For cognition, the pooled **CDR-SB score was 0.19 points higher** with BACE1 inhibitors (95% CI 0.10 to 0.28) — indicating slightly worse cognition than placebo. MMSE (−0.12, 95% CI −0.31 to 0.06) and ADAS-Cog-11 (0.56, 95% CI −0.12 to 1.24) trended in the same unfavourable direction but did not reach statistical significance.

Safety analysis showed significantly increased risk across almost every category examined — including serious TEAEs, hepatic enzyme elevations (ALT and AST), neuropsychiatric events, sleep disturbances, diarrhoea and rashes. Only all-cause mortality showed no significant difference between groups (full estimates in the table).

POOLED OUTCOMES

EFFICACY — Mean Difference	
Outcome	MD (95% CI)
CDR-SB	0.19 (0.10, 0.28) ↑
MMSE	−0.12 (−0.31, 0.06) NS
ADAS-Cog-11	0.56 (−0.12, 1.24) NS
SAFETY — Risk Ratio (RR > 1 = higher risk)	
Adverse event	RR (95% CI)
≥1 TEAE	1.07 (1.05, 1.08)
≥1 serious TEAE	1.21 (1.11, 1.33)
Increased ALT	2.19 (1.80, 2.66)
Increased AST	2.57 (2.04, 3.25)
Neuropsychiatric events	1.59 (1.40, 1.80)
Sleep disturbances	1.84 (1.57, 2.15)
Diarrhoea	1.58 (1.35, 1.85)
Rashes	2.00 (1.52, 2.62)
Hair colour changes	15.76 (7.48, 33.21)
Mortality	1.13 (0.69, 1.85) NS

Bold = statistically significant (95% CI excludes the null). ↑ CDR-SB indicates significantly worse cognition vs placebo. NS = not significant.

LIMITATIONS

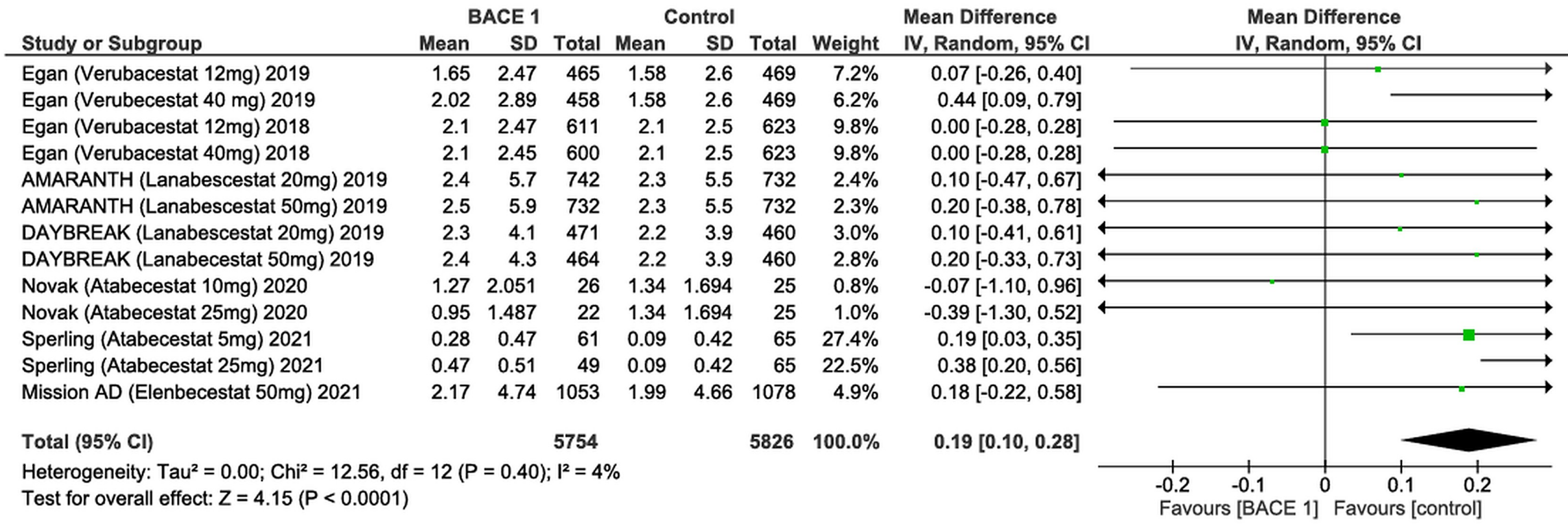
Different agents & doses. Trials evaluated several BACE1 inhibitors (verubecestat, lanabecestat, atabecestat, elenbecestat) at various doses, adding clinical heterogeneity.

Statistical heterogeneity. Some cognitive outcomes were highly heterogeneous (ADAS-Cog-11, I² = 82%).

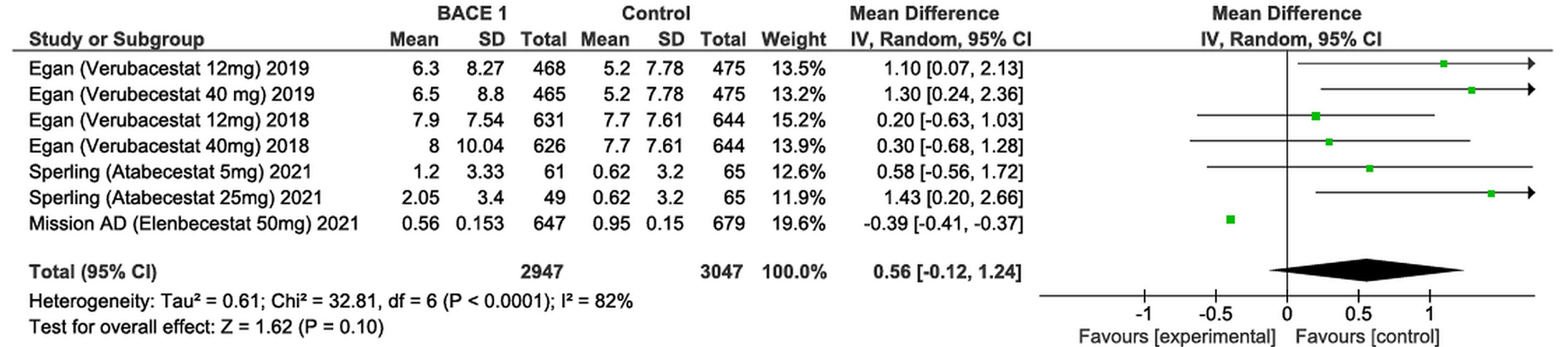
Early termination. Several trial programmes were stopped early for futility or safety, which may limit long-term estimates.

FOREST PLOTS

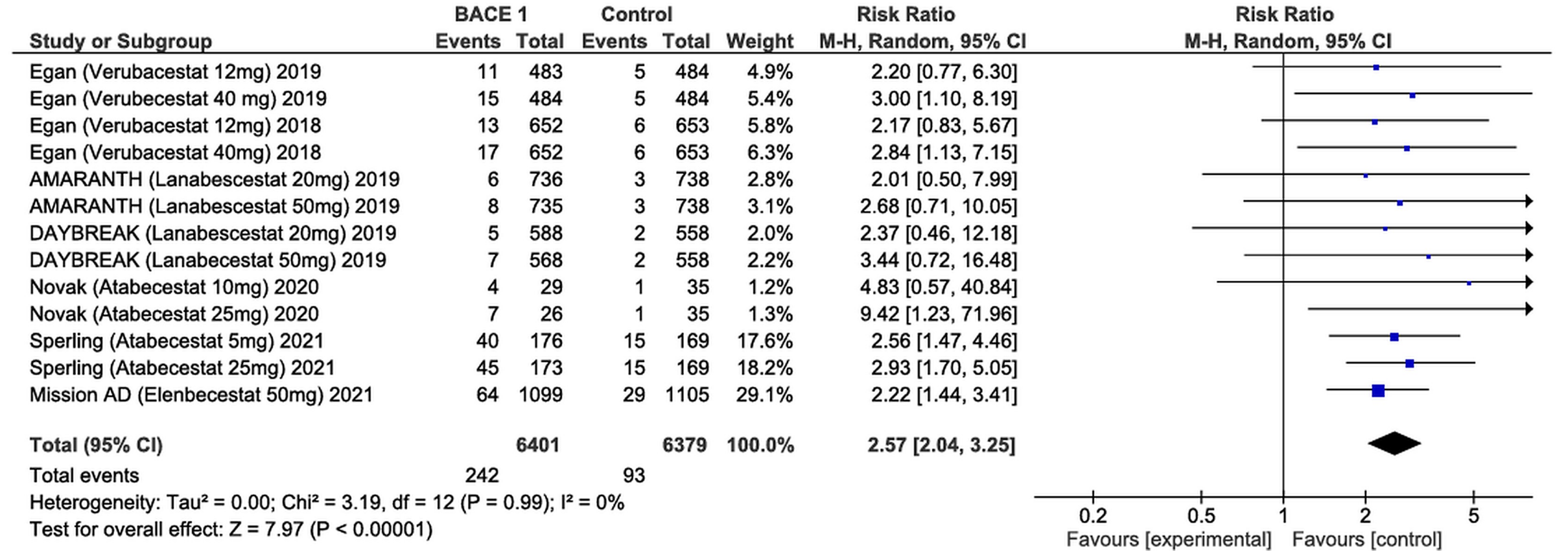
Pooled mean difference of ADAS-Cog-11 score



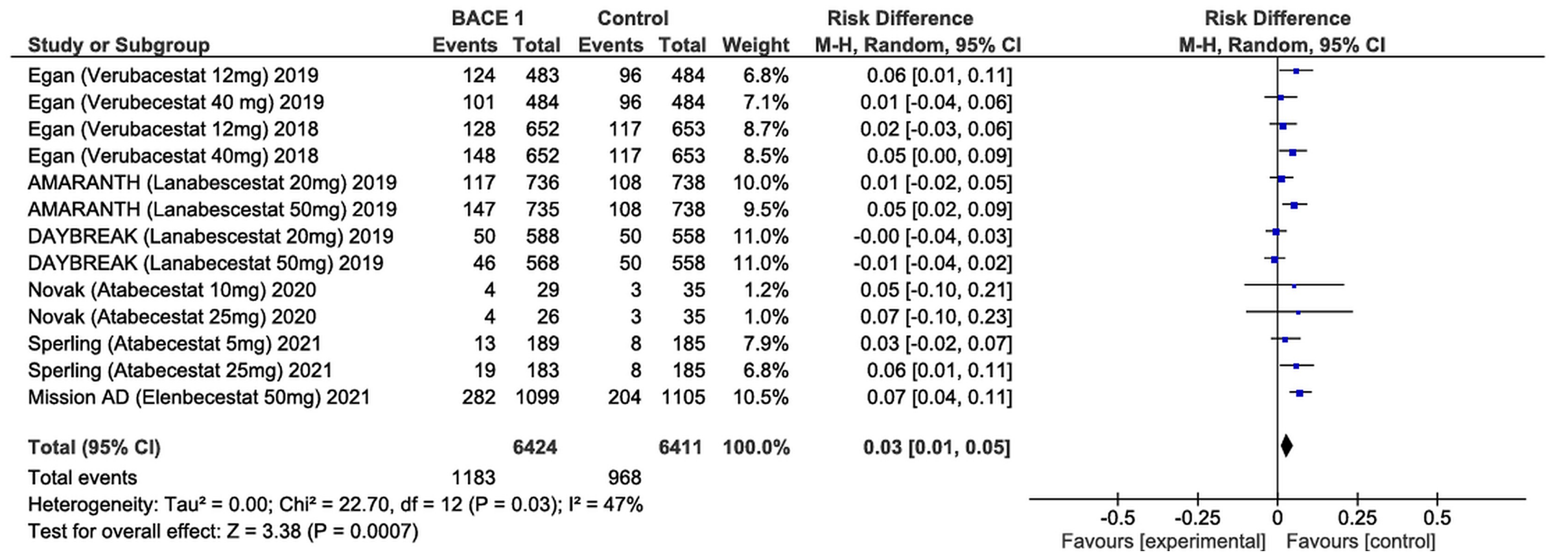
Pooled mean difference of CDR-SB score



Pooled risk ratio of increased AST



Pooled risk ratio of ≥1 serious TEAE



REFERENCES

- Egan MF, Kost J, Voss T, et al. Randomized trial of verubecestat for prodromal Alzheimer's disease. N Engl J Med. 2019;380(15):1408–20. doi:10.1056/NEJMoa1812840.
- Wessels AM, Tariot PN, Zimmer JA, et al. Efficacy and safety of lanabecestat for early and mild Alzheimer disease: the AMARANTH and DAYBREAK-ALZ randomized clinical trials. JAMA Neurol. 2020;77(2):199–209. doi:10.1001/jamaneurol.2019.3988.
- Novak G, Streffer JR, Timmers M, et al. Long-term safety and tolerability of atabecestat (UNJ-54861911), an oral BACE1 inhibitor, in early Alzheimer's disease spectrum patients. Alzheimers Res Ther. 2020;12(1):58. doi:10.1186/s13195-020-00614-5.
- Sperling R, Henley D, Aisen PS, et al. Efficacy, safety, and biomarker outcomes of atabecestat in preclinical Alzheimer disease: a truncated randomized phase 2b/3 trial. JAMA Neurol. 2021;78(3):293–301. doi:10.1001/jamaneurol.2020.4857.