

Quantification of Benefit-Risk in Amyloid-Targeting Therapies for Cognitively Unimpaired Alzheimer's Disease

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OBJECTIVES

- Quantify the effect of variations in amyloid-targeting therapy (ATT) attributes on preferences among cognitively unimpaired adults aged ≥50 years.
- Measure acceptable trade-offs between ATT attributes that adults aged ≥50 years consider meaningful, relative to treatment risks.

CONCLUSIONS

- The majority of cognitively unimpaired adults aged ≥50 years preferred ATT over no treatment.
- Disease-modifying benefit – **delaying progression to Alzheimer's disease with mild cognitive impairment (AD with MCI)** – was the key driver of treatment preferences, outweighing both Amyloid Related Imaging Abnormalities (ARIA) risk and ARIA resolution time.
- Overall, ATTs demonstrated a favorable net benefit–risk balance, with **perceived benefits outweighing treatment-related risks**.
- This study is ongoing; full results will be disclosed at a later date.

BACKGROUND

- Alzheimer's disease (AD) pathology begins years before the onset of cognitive symptoms.¹
- Amyloid-targeting therapies (ATTs) are being evaluated for use in cognitively unimpaired AD to delay progression to AD with MCI and AD with dementia.^{2,3}
- ATTs may offer clinical benefits, including delayed disease progression, but are also associated with risks, such as ARIA (an abnormal brain scan)⁴, requiring individuals to make trade-offs when considering initiation of ATT.
- Understanding whether individuals would initiate treatment and how they weigh potential benefits relative to treatment risks can inform clinical discussions and policy decisions.

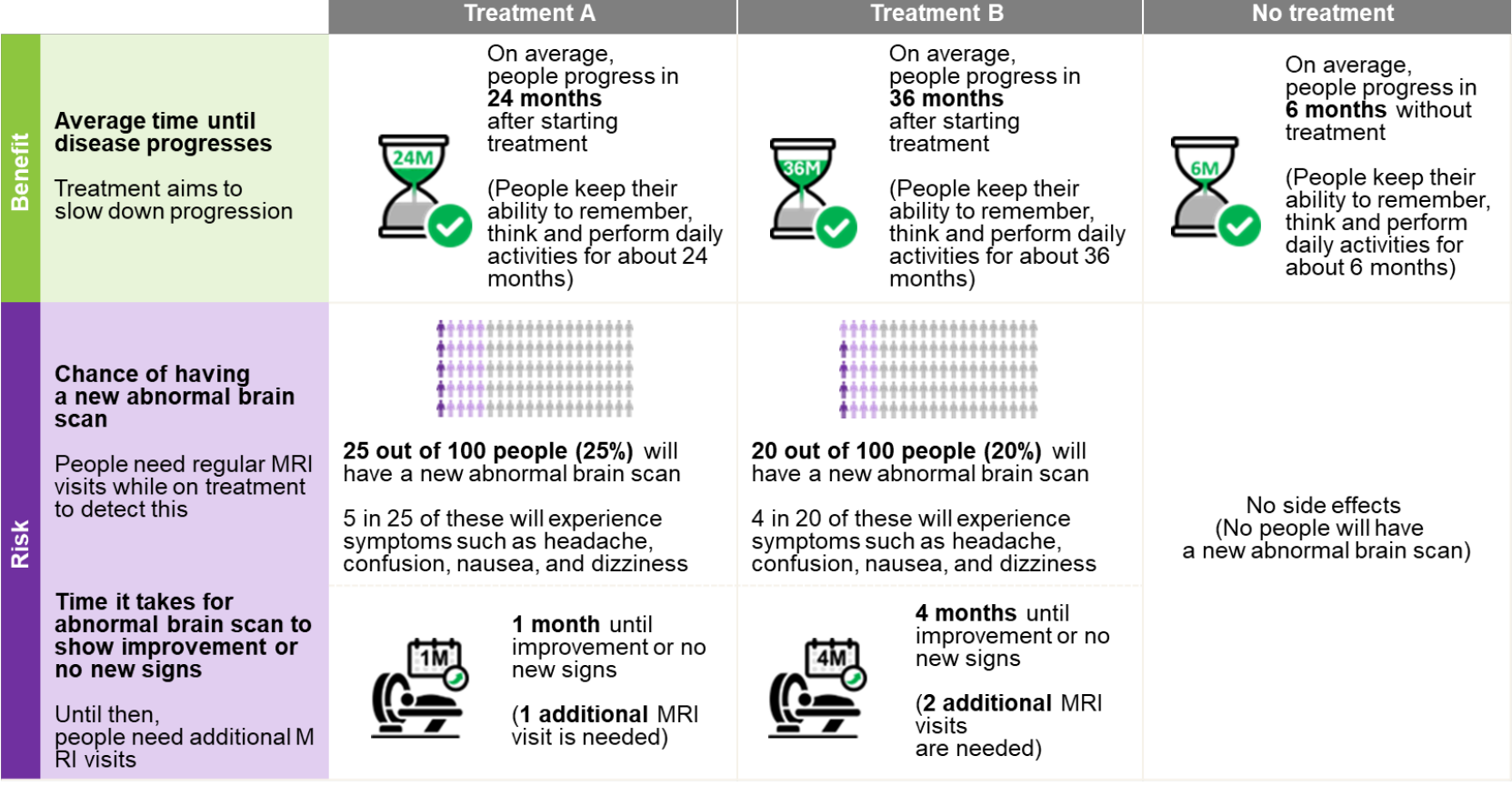
Study Aim

- This study aimed to elicit preferences for ATTs and assess whether the perceived benefits of ATTs outweigh their risks using a preference-based benefit-risk assessment based on a discrete choice experiment (DCE).
- The DCE was administered online among adults aged ≥50 years in the United States (US), United Kingdom (UK), Germany, and Japan without cognitive impairment (e.g., AD with MCI or AD with dementia).

STUDY DESIGN

- Participants were asked to imagine they had evidence of amyloid plaque burden in the brain but were cognitively unimpaired and were considering treatment options that aim to delay progression to AD with MCI.
- Participants completed 9 DCE choice tasks, choosing among three options described by average time to or probability of progression to AD with MCI (at 2 and 3 years, each), ARIA risk, which included symptomatic and asymptomatic ARIA and ARIA resolution time, with their levels systematically varied within clinically plausible ranges (**Figure 1**).
- To minimize conceptual overlap among the three benefit attributes, an implicit partial-profile DCE design was used, whereby only one benefit attribute was displayed alongside two risk attributes in each choice task, with benefit attributes rotated across tasks.

Figure 1. Example Choice Task



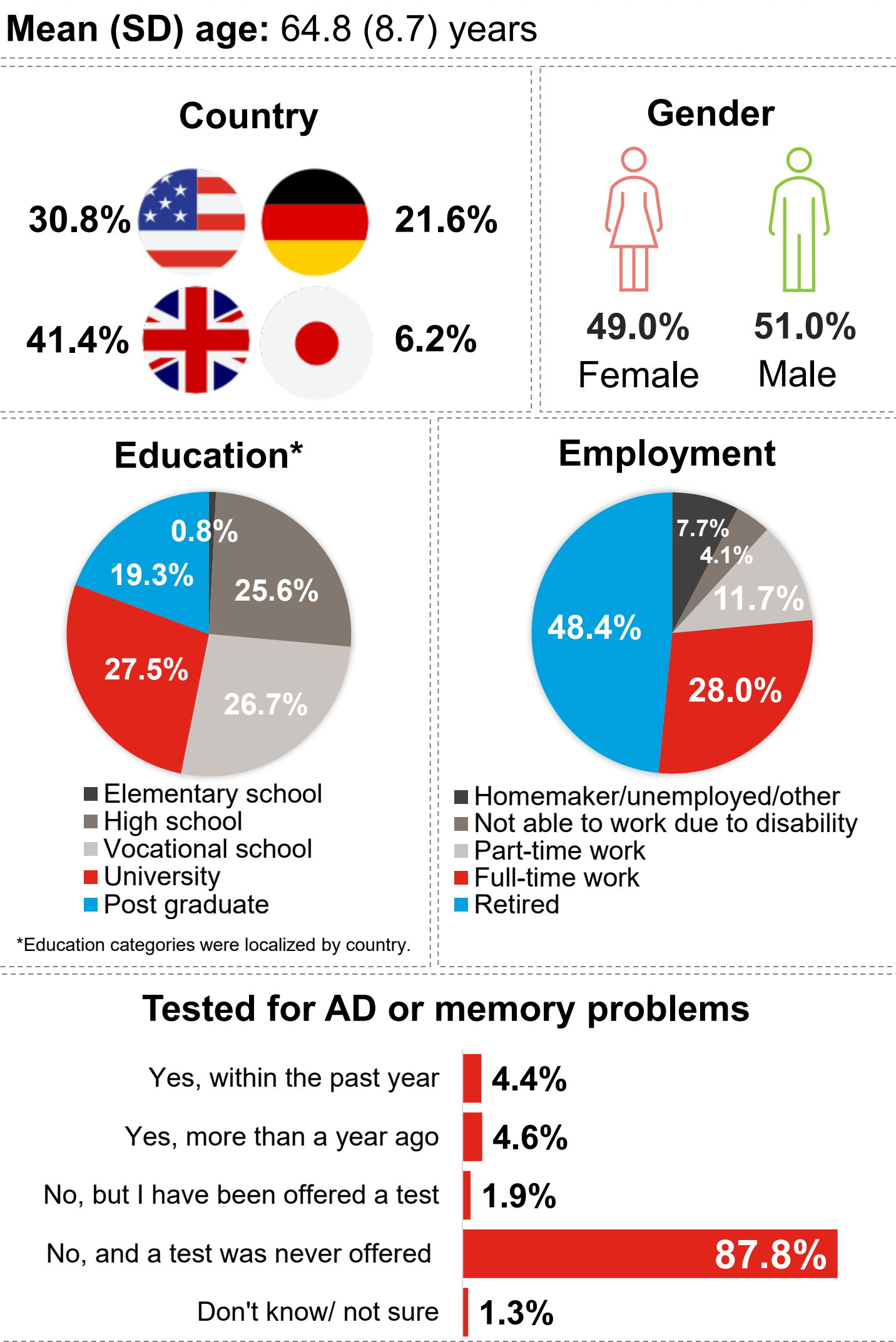
*A survey design refinement informed by the quantitative pilot occurred and included removal of a treatment arm in the final DCE design.

Statistical Analysis

- DCE choice data were analyzed using a mixed logit model to estimate relative attribute importance (RAI) and maximum acceptable risk (MAR) of ARIA required in exchange for benefit gain.
- A clinically plausible, hypothetical ATT profile was used to estimate net benefit-risk against no treatment, incorporating RAI from DCE.

RESULTS

Participant characteristics (N=2239)



Acknowledgments:
Medical writing was provided by Louisa Ludwig-Begall, PhD (PPD clinical research business of Thermo Fisher Scientific) and Evangeline Ann Daniel (Eli Lilly and Company) in accordance with Good Publication Practice guidelines and was funded by Eli Lilly and Company.

Disclosures:
Oralee Johnson Varnado, Antje Tockhorn-Heidenreich, Nalin Payakachat, Alice Farquharson, and J. Scott Andrews: Employee of Eli Lilly and Company and minor shareholder. Matthew Quaife and Jaein Seo: Employee of Thermo Fisher Scientific and minor shareholder. Yasmijn Slaghekke and Álvaro Alberto Gutiérrez-Vargas: Employee of Thermo Fisher Scientific. Niklas Mattsson-Carlgren: Has received speaker/consultancy fees from BioArctic, Biogen, Eli Lilly, Merck, Novo Nordisk, Owkin, Positriga and Roche.

KEY RESULT

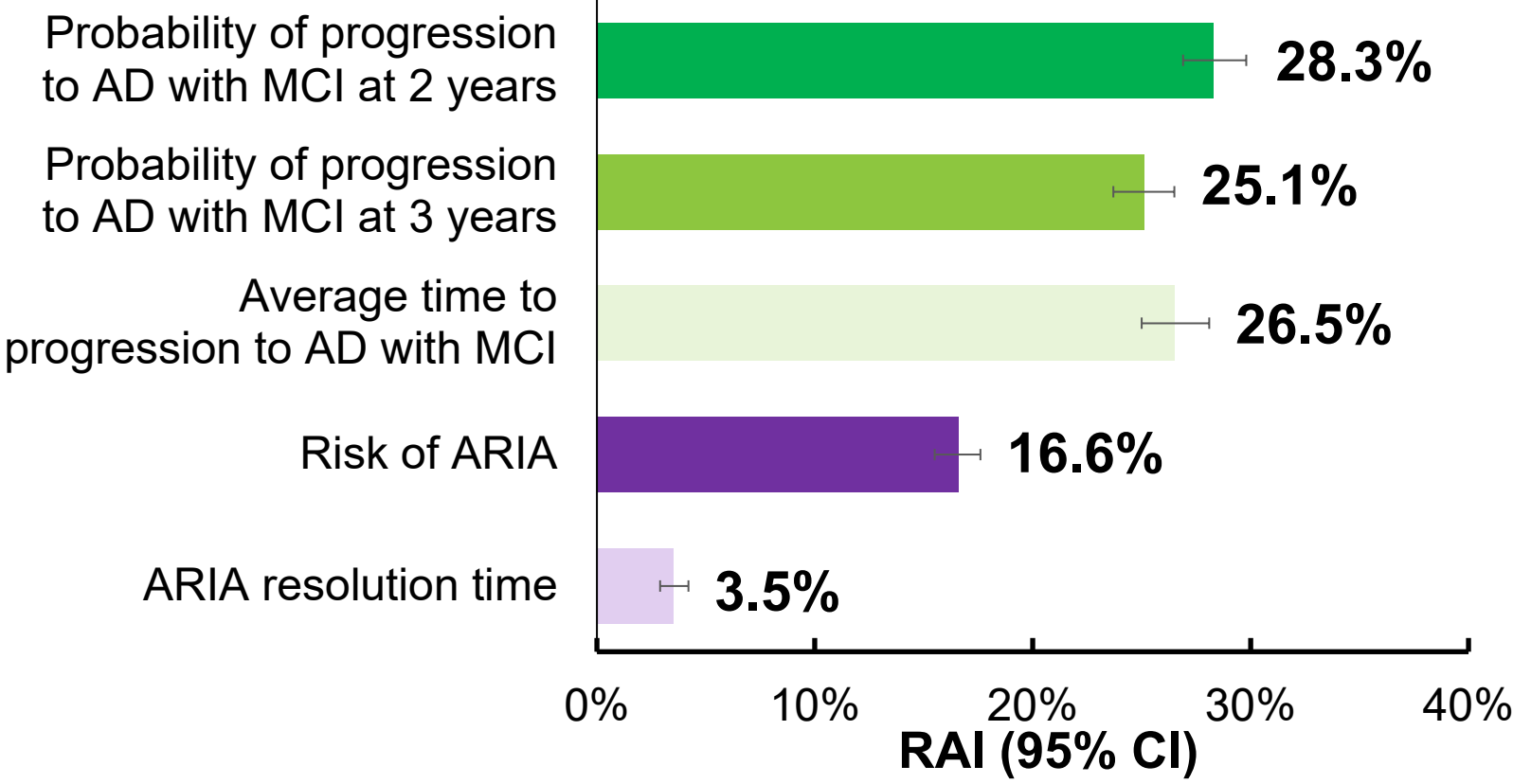
Choosing Treatment

- Across the choice tasks, 38.2% of participants never opted out of treatment.
- Participants were significantly more likely to choose a treatment option (A or B) rather than opting out ($p < 0.001$).

Relative attribute importance

- Once opting in, treatment choices were influenced by ATT attributes to varying extents.
- Treatment benefits related to delaying progression to AD with MCI were the most influential drivers of treatment preference, with similar importance across the three benefit attributes (**Figure 2**).
- Risk-related attributes were less influential in treatment decision-making, including chance of having an abnormal brain scan (16.6%) and time until abnormal brain scan improvement or no new signs (3.5%).

Figure 2. Relative Importance of ATT Attributes

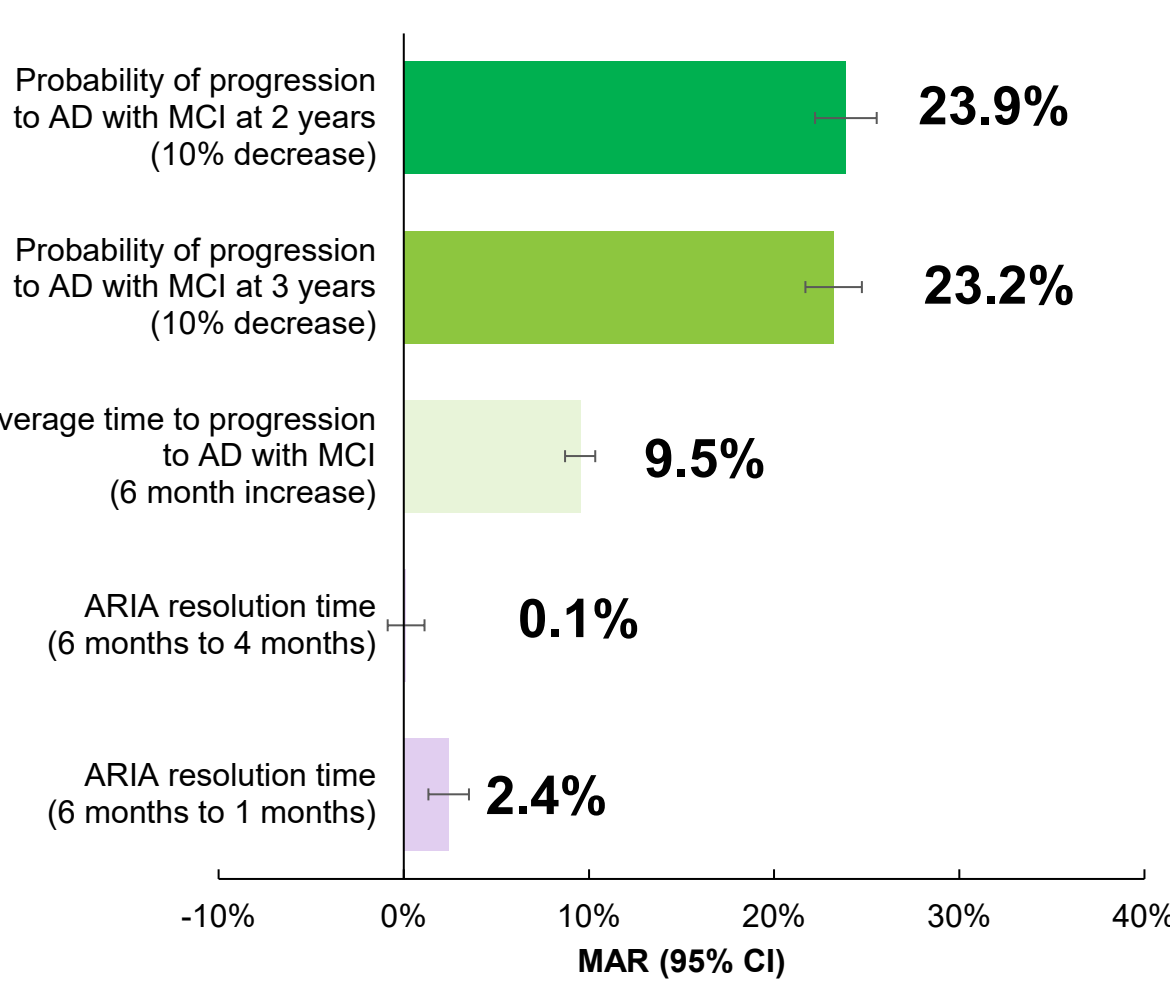


Abbreviation: AD with MCI, Alzheimer's disease with mild cognitive impairment; ARIA, Amyloid Related Imaging Abnormalities; CI, confidence interval; RAI, Relative attribute importance.

Maximum Acceptable Risk of ARIA

- For a treatment that reduces the probability of progression to AD with MCI by 10% at 2 and 3 years, participants were willing to accept a 23.9% and 23.2% increase, respectively, in the risk of ARIA.
- For a treatment that delays progression to AD with MCI by 6 months, participants were willing to accept a 9.5% increase in the risk of ARIA.
- To reduce the ARIA resolution time from 6 months (+3 MRI scans) to 1 months (+1 MRI scan), participants were willing to accept 2.4% increase in the risk of ARIA.
- A shorter ARIA resolution time with associated monitoring was not a meaningful driver in treatment decision making.

Figure 3. Maximum Acceptable Risk of ARIA

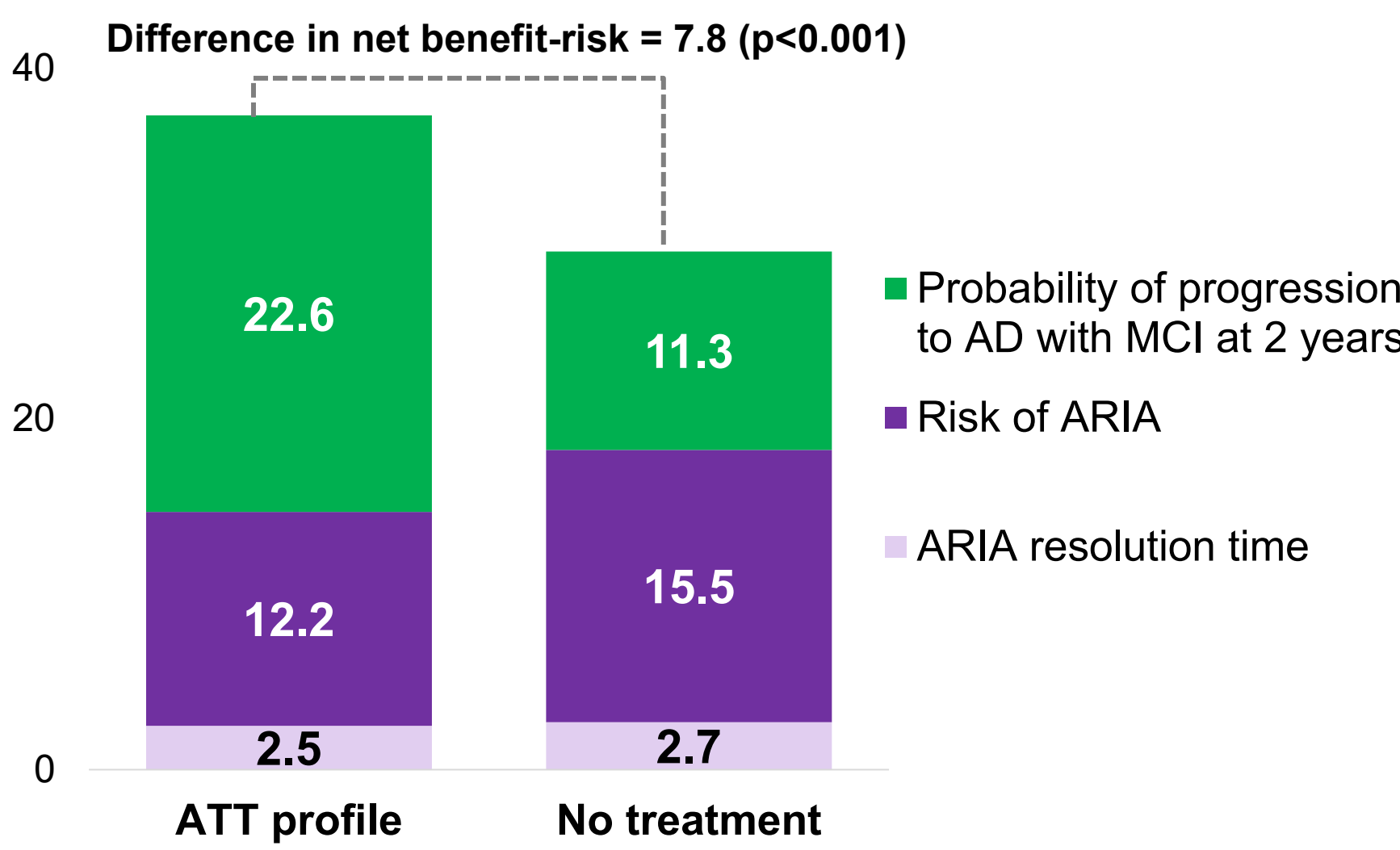


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Preference-based Benefit-Risk Assessment

- The ATT profile was preferred over no treatment (**Figure 4**).
- The ATT profile was perceived to have benefits that outweigh its risks, with a significantly higher net benefit-risk score than the no-treatment profile (37.3 vs 29.6; difference = 7.8; $p < 0.001$).
- The largest contributors to the net benefit-risk score were reductions in probability of progression to AD with MCI at 2 years, while risk-related attributes negatively contributed to overall benefit-risk.

Figure 4. Net Benefit-Risk



Abbreviations: ATT, amyloid-targeting therapy; AD with MCI, Alzheimer's disease with mild cognitive impairment. A two-sided z-test with a significance level of 5% was used to assess the difference in net benefit risk. To avoid double-counting of correlated efficacy benefits in the benefit-risk assessment, only the benefit attribute with the highest RAI, probability of progression to AD with MCI at 2 years, was included in the net benefit-risk estimation. Clinical performance values were assumed to be 8.0% (ATT profile) and 2.0% (no treatment) for the chance of having an abnormal brain scan (risk of ARIA), 10.0% (ATT profile) and 20.0% (no treatment) for the probability of progression to AD with MCI at 2 years, and 2.4 months (ATT profile) and 2.1 months (no treatment) for the chance it takes for an abnormal brain scan to show improvement or no new signs (ARIA resolution time).

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