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Letter to the Editor

The generalizability gap: anticoagulant exclusions and the "Enhanced Safety" of donanemab in the EU-eligible population

Dear Editor,

We read with interest the recent article by Jessen et al. [1] reporting the efficacy and safety of donanemab in the European Union (EU)-eligible population from the TRAILBLAZER-ALZ 2 trial. The authors should be commended for applying the European Medicines Agency-requested conservative hybrid imputation approach and for providing clinically relevant data to inform regulatory implementation.

However, we are concerned that the reported "enhanced safety profile" and "manageable" incidence of amyloid-related imaging abnormalities (ARIA) in the EU-eligible population should be interpreted with caution, as these findings may partly reflect restrictive eligibility criteria rather than improved real-world tolerability.

By design, the EU-eligible population excluded patients receiving anticoagulant therapy [1]. While this exclusion may reduce the occurrence of ARIA-H and macrohemorrhage during the trial, it introduces an important limitation in external validity. Atrial fibrillation (AF), the leading indication for anticoagulant use in older adults, frequently coexists with dementia and has been associated with an increased risk of cognitive decline and incident dementia [2]. Furthermore, growing evidence suggests that anticoagulation constitutes an important component of routine management in this population because adequate anticoagulant treatment in AF may influence long-term cognitive outcomes and dementia progression [3]. Consequently, excluding anticoagulated individuals may create a study population that differs substantially from patients encountered in routine Alzheimer's disease (AD) practice.

This concern is not merely theoretical. Population-based data indicate that oral anticoagulant use is common among patients with AD. In a nationwide Finnish cohort of over 70,000 individuals with clinically verified AD, the prevalence of oral anticoagulant use at the time of AD diagnosis was approximately 23% [4]. Atrial fibrillation was the most common comorbidity among these anticoagulant users. Similarly, a meta-analysis of 27 studies found that people with cognitive disorders and AF had 52% lower odds of receiving oral anticoagulants compared to those without cognitive impairment, highlighting both the high prevalence of the indication and the existing treatment gap [4]. These figures suggest that the anticoagulant exclusion in TRAILBLAZER-ALZ 2 may have removed a clinically significant segment of the real-world AD population.

It is also important to note that while the EU-eligible population excluded three specific contraindications; superficial siderosis, anticoagulant use, and uncontrolled hypertension [1]. Anticoagulation is arguably the most prevalent and clinically consequential of these in routine practice. The other two exclusions, while valid, affect a smaller proportion of the AD population. The selective removal of anticoagulated patients therefore exerts a disproportionate influence on the generalizability of the safety findings.

Therefore, the favorable safety outcomes observed in the EU-eligible subgroup may not necessarily indicate universally improved safety but rather reflect outcomes within a selectively lower-risk cohort. This distinction is particularly important when translating trial findings into everyday clinical decision-making. Clinicians in Europe will inevitably encounter anticoagulated patients with early symptomatic AD who meet all other eligibility criteria but are precluded from donanemab therapy based on the label. The trial data offer no direct evidence on ARIA risk, macrohemorrhage rates, or overall tolerability in this substantial subgroup.

Future studies and post-marketing investigations should evaluate anti-amyloid therapies in broader and more representative populations, including patients receiving anticoagulation therapy. Dedicated real-world safety analyses are needed to determine whether the observed safety profile of donanemab remains consistent across the full spectrum of patients with AD. Only then can clinicians and regulators make fully informed benefit–risk assessments for the population that actually presents in clinical practice.

Ethics approval

Not applicable.

Declaration of generative AI and AI-assisted technologies in writing process

During the preparation of this letter, the authors used a generative AI assistant for structural editing of the manuscript. The authors reviewed, critically evaluated, and substantially revised all AI-generated content, and take full responsibility for the accuracy, integrity, and final content of this publication.

CRediT authorship contribution statement

Azan Ijaz: Conceptualization, Writing – original draft. **Ghulam Mohyudin:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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