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None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Table S1. Characteristics of patients who completed cognitive behavioral therapy for insomnia.

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"Real world" eligibility for aducanumab

To the Editor:

On June 7, 2021, the U.S. Food and Drug Administration (FDA) approved aducanumab, an amyloid beta-directed monoclonal antibody, as a new treatment for Alzheimer's disease (AD),[1] taking advantage of an Accelerated Approval program. The aducanumab effect on amyloid beta plaques[2] was deemed to predict benefits for patients and, thus, considered as an approvable surrogate endpoint. Nevertheless, there are residual uncertainties concerning the clinical effectiveness of the drug[3–5] that has to be confirmed via post-approval phase 4 studies.

As often happening in the design of randomized controlled trials (RCTs), relatively rigid eligibility criteria were adopted in the EMERGE [NCT02484547] and ENGAGE [NCT02477800] phase 3 studies on aducanumab to render more homogeneous the sampled populations. The choice was aimed at reducing the established clinical and biological heterogeneity of the target conditions (i.e., mild cognitive impairment [MCI] and mild AD dementia) and reduce safety/tolerability concerns. At the same time, the stringent criteria may result in the recruitment of patients who are not adequately representative of the overall clinical population, consequently reducing the generalizability of the findings.[6] A poor external validity was already documented for the trials leading to the approval of the pharmacological compounds currently marketed for the symptomatic treatment of AD.[7,8]

To identify the proportion of patients who would be potentially eligible to receive aducanumab in the "real world", we systematically applied the criteria adopted in the pre-approval research protocols to a representative clinical population referring to a geriatric outpatient unit of a tertiary university hospital in Milan (Italy). A

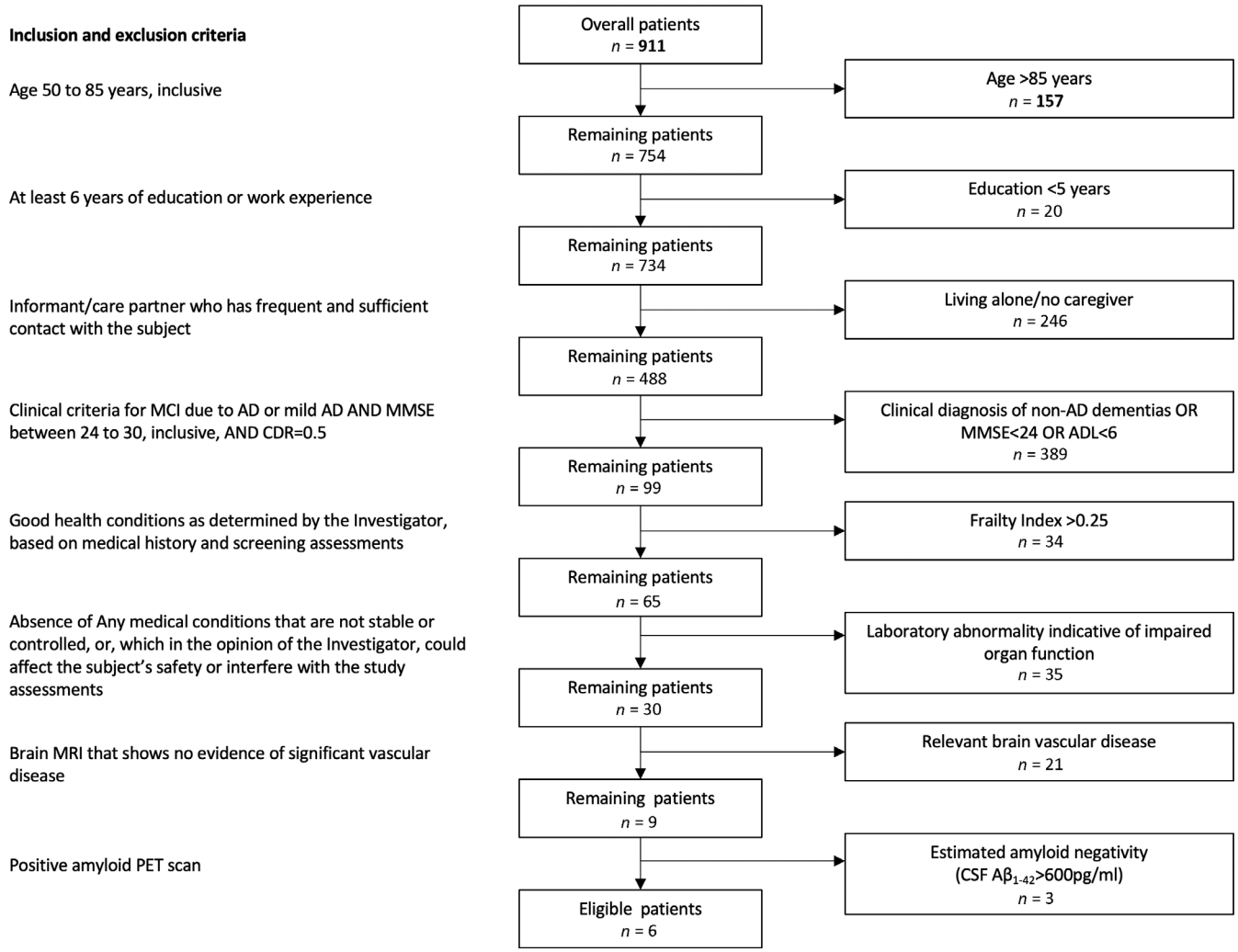

FIGURE 1 Application of the EMERGE and ENGAGE eligibility criteria to real-world patients attending a university memory clinic

total of 911 patients consecutively attending the unit for cognitive complaints were considered. Patients underwent a comprehensive geriatric assessment, including cognitive and neuropsychological evaluation, frailty assessment (using a 40-item Frailty Index [FI]), routine blood tests, and neuroimaging, as part of standard clinical care. In addition, a minority of these patients (i.e., 11.4%) underwent a lumbar puncture to measure cerebrospinal fluid (CSF) AD biomarkers (i.e., $A\beta_{1-42}$, total-tau, and phospho-tau). The diagnoses of MCI, AD dementia, and non-AD dementias were formulated according to current international diagnostic criteria. The local Ethics Committee authorized the data collection and use as part of a clinical registry. Written informed consent was obtained from patients (or proxies as appropriate).

The inclusion and exclusion criteria of the EMERGE and ENGAGE studies were retrieved from the information registered on the clinicaltrials.org database. These criteria were then operationalized in our clinical database and sequentially applied to the patients to test their potential eligibility to aducanumab.

About half of the patients ($n = 423$) resulted ineligible due to age >85, <6 years of education, and absence of a formal caregiver (Figure 1). Another relevant part of patients ($n = 389$) would then be excluded because of not meeting the prespecified clinical criteria (e.g., diagnosis of non-AD dementia, Mini-Mental State Examination score <24, and/or evident functional impairment). Most of the remaining subjects ($n = 99$) would not probably be selected because they were frail (i.e., FI >0.25,[9] thus not in the "good health" conditions as required), presenting a major laboratory abnormality, underweight/obesity, or significant brain vascular disease at the neuroimaging. Finally, given that nearly one-third of the patients with MCI or AD in our population did not exhibit a CSF positive amyloid status (i.e., $A\beta_{1-42} < 600$ pg/ml[10]), we assumed that three additional subjects would possibly be excluded because they

result negative at the amyloid-beta measurement. Thus, only six patients (i.e., 0.66%) of the study population would potentially be candidates to aducanumab.

Our findings should be cautiously interpreted since they were derived from a single center experience and obtained by adapting the research criteria to the data routinely collected as part of the clinical activities. Moreover, the eligibility criteria applied in our analyses were those retrieved from clinicaltrial.gov. We cannot be sure that some modifications have been used in the conduction of the EMERGE and ENGAGE studies since no article from these trials has yet been published in a peer-reviewed journal.

Our results suggest that only a marginal proportion of patients with cognitive disorders currently attending "real-world" geriatric services would potentially benefit from aducanumab due to the low external validity of pre-approval studies. This observation, together with the unanswered questions concerning the aducanumab efficacy and cost-effectiveness,[11,12] should be considered before planning any reorganization and redistribution of care resources.

In this context, the final indications provided by the FDA will be critical. In the original version of the prescribing information for aducanumab (marketed as Aduhelm), the FDA did not limit its use to only mild cases but included all the AD stages.[13] Moreover, different from the phase 3 RCTs, no exclusion criterion based on age, concomitant diseases, or therapies was mentioned. In a revised more stringent indication, the use was limited to MCI and mild AD dementia.[14] If applied to our registry, these two FDA indications would make eligible 392 (i.e., 43.0%) and 311 (i.e., 34.1%) patients, respectively. In other words, the FDA criteria determine a 65-fold and 52-fold increase of the number of potential candidates compared with what was designed in the EMERGE and ENGAGE trials. It is thus clear how the resulting gap between the research and "real world" fields is massive, exemplifying once again the "evidence-based medicine issue" challenging decisions in geriatric care.[7]

CONFLICT OF INTEREST

Authors have no competing interest to disclose for the present study.

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AUTHOR CONTRIBUTIONS

Marco Canevelli: study conception and design, and writing of the manuscript. Paolo Dionigi Rossi: data collection, interpretation of data, and drafting of the manuscript. Paolo Astrone: data collection. Ernesto Consorti: data collection. Nicola Vanacore: interpretation of data and drafting of the manuscript. Matteo Cesari: study conception, interpretation of data, and drafting of the manuscript.

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