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REVIEW

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Navigating the introduction of anti-amyloid therapy in Europe: a position statement by individual members of the EADC

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Abstract

Introduction Anti-amyloid antibodies for the treatment of Alzheimer´s disease (AD) are currently being evaluated for approval and reimbursement in Europe. An approval brings opportunities, but also challenges to health care systems across Europe. The objective of this position paper is to provide guidance from experts in the field in terms of navigating implementation.

Methods Members of the European Alzheimer's Disease Consortium and a representative of Alzheimer Europe convened to formulate recommendations covering key areas related to the possible implementation of anti-amyloid antibodies in AD through online discussions and 2 rounds of online voting with an 80% threshold for a position to be accepted.

Results In total, 24 recommendations were developed covering the research landscape and priorities within research in AD following a possible approval, potential impact on health care systems and diagnostic pathways, and communication to patients about anti-amyloid antibodies. Anti-amyloid antibodies are regarded as a substantial innovation with an important clinical impact. In addition, however, new compounds with other mechanisms of action and/or route of administration are also needed. Approval of new treatments will require changes to existing patient pathways and real-world data needs to be generated.

Conclusion Comprehensive guidance is provided on the potential implementation of anti-amyloid antibody therapies in Europe following possible approval. Emphasis is placed on the necessity of regularly updating recommendations as new evidence emerges in the coming years.

Keywords Alzheimer´s disease, Anti-amyloid antibodies, Recommendations, Mild cognitive impairment

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Introduction

Since the formulation of the amyloid cascade hypothesis in the early 1990 s [1], significant efforts have been directed towards the development and introduction of drugs aimed at reducing beta-amyloid, with the goal of eliciting clinically meaningful and disease-modifying effects in Alzheimer's disease (AD) [2]. Various compounds employing different mechanisms to prevent formation or to lower beta-amyloid, including monoclonal antibodies targeting different forms of beta-amyloid, have undergone testing in drug trials [3]. Against the backdrop of previous trial failures with other amyloid-lowering antibodies, which included negative phase III trials, three antibodies—Aducanumab [4], Lecanemab [5], Donanemab [6] have received Food and Drug Administration (FDA) approval in the United States for early AD (https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug; https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-treatment-adults-alzheimers-disease; https://www.fda.gov/news-events/press-announcements/fda-converts-novel-alzheimers-disease-treatment-traditional-approval). In November 2024, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave a positive opinion to grant approval of Lecanemab for the European Union (https://www.ema.europa.eu/en/medicines/human/EPAR/leqembi).

In the U.S., Aducanumab gained approval through the accelerated approval pathway (https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug.). However, in early 2024, the manufacturer stopped marketing and all post marketing activities for Aducanumab and returned the rights on the compound back to, which initially had developed the drug (https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval.). According to the manufacturer, this was not due to safety or efficacy concerns but to reprioritize resources within their AD clinical development program (https://investors.biogen.com/news-releases/news-release-details/biogen-realign-resources-alzheimers-disease-franchise.). The marketing approval application for Aducanumab had earlier been withdrawn in Europe after EMA advice (https://www.ema.europa.eu/en/medicines/human/EPAR/aduhelm.). In July 2023, Lecanemab received full FDA approval (https://www.fda.gov/news-events/press-announcements/fda-converts-novel-alzheimers-disease-treatment-traditional-approval.), supported by data from a confirmatory phase III trial in 2022 showing consistent significant effects across primary and secondary outcomes, including imaging and various fluid biomarkers as well as clinically relevant outcome measures like cognition and function, and also care giver burden and quality of life [5] and since then in China, South Korea, Japan, the UK and other countries (https://investors.biogen.com/news-releases/news-release-details/leqembir-lecanemab-approved-treatment-alzheimers-disease-china.). In July of 2024, the CHMP gave a negative opinion for Lecanemab, which was appealed by the manufacturer. After re-examining its initial opinion, EMA's CHMP has recommended granting a marketing authorisation to Lecanemab for treating mild cognitive impairment or mild dementia due to AD (early AD) in a restricted population of patients, who have only one or no copy of ApoE4. ApoE4 is the haplotype of apolipoprotein E, which carries a higher risk for amyloid-related imaging abnormalities (ARIA) for patients under treatment with Lecanemab and other amyloid antibodies. The CHMP further concluded that risk minimization measures must be in place to reduce the risk of severe and symptomatic ARIA and monitor its consequences in the long term. This includes a controlled access program to ensure that the medicine is used only in the recommended patient population. Additionally, patients need to undergo regular MRI scanning to monitor for ARIA and additional MRI scans if patients develop symptoms of ARIA. In addition, it must carry out a post-authorization safety study and set up an EU-wide registry study to further characterize ARIA-E and ARIA-H and assess the effectiveness of the risk minimization measures (https://www.ema.europa.eu/en/medicines/human/EPAR/leqembi.). Due to an update as of 28 January 2025, the European Commission has asked the CHMP as part of its decision-making process to consider information on the safety of Leqembi that became available after the adoption of the CHMP opinion in November 2024 and whether this may require an update of the opinion. The Commission also asked the CHMP to consider whether the wording of the risk minimization measures is clear enough to ensure correct implementation (https://www.ema.europa.eu/en/documents/medicine-qa/questions-answers-approval-marketing-authorisation-leqembi-lecanemab_en.pdf.). Donanemab, with efficacy indications comparable to Lecanemab, is also under EMA review for licensing approval in the EU. In the US, the FDA first delayed a decision on Donanemab, in order to further understand the safety results and the efficacy implications of the unique trial design of the TRAILBLAZER-ALZ 2 study, namely its limited-duration dosing regimen that allowed patients to complete treatment based on an assessment of amyloid plaque and the inclusion of participants based on tau levels [6]. Klik eller tryk her for at skrive tekst. After this, the FDA approved Donanemab (https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-treatment-adults-alzheimers-disease.). Donanemab

has also been approved in the UK but with restrictions so that Donanemab is not indicated in patients who are APOE-e4 homozygous, have cerebral amyloid angiopathy or are on anticoagulants (https://www.gov.uk/government/news/donanemab-licensed-for-early-stages-of-alzheimers-disease-in-adult-patients-who-have-one-or-no-copies-of-apolipoprotein-e4-gene.). As outlined above, the pathway for all three antibodies from readout of phase III results to approval has been convoluted and littered with obstacles, specifically within the EU, usually not encountered in other therapeutic areas. This may both arise from stakeholders not viewing AD as a healthcare priority [7], from discussions on defining, which effect size confers clinically relevance and the resulting risk/benefit ratio or the potential societal economic impact of implementing the treatment [8].

Anticipated results from confirmatory trials with other compounds in the coming years [2] heighten the likelihood of other disease-modifying therapies (DMT) for early AD receiving approval in Europe. While a potential DMT brings considerable optimism to patients and offers significant benefits, implementing antibody treatments will necessitate additional resources, capacity of the system and adjustments to current diagnostic and care pathways. Considering these challenges, individual principal investigators of members sites of the European Alzheimer's Disease Consortium (EADC), comprising expert centers in Europe that diagnose, treat and monitor patients with AD and other neurodegenerative conditions, and conduct clinical research, and a representative of Alzheimer Europe convened to draft statements addressing these issues. This publication expresses the view of the authors and not necessarily of all EADC members sites. While this paper primarily delves into anti-amyloid antibody therapy, its insights extend to disease-modifying therapies (DMTs) employing alternative mechanisms of action and diverse operational protocols.

Methods

A group of experts in clinical Alzheimer's research and care, whose academic institutions are members of the EADC, and a representative of Alzheimer Europe were invited to contribute to the creation of a position paper. Out of the 22 individuals invited, 20 actively participated and collaborated in the process as co-authors. One participant voted on the statements and agreed to the adopted positions but did not consent to be listed as a co-author due to disagreement regarding wording outside the recommendations. Due to an emergent possible conflict of interest, a second person left the project, leaving a total of 19 voters. Initially, a steering committee, consisting of three members (KF, LF, FJ), proposed overarching topics for consideration. These topics were then circulated among members through an online survey, encouraging feedback. If there was consensus or minor dissent, which could be resolved through discussion, the topic proceeded for further consideration. At this stage, a rigid cut-off for consensus was not applied. Subsequently, two online meetings were conducted to facilitate the exchange of viewpoints and discussions. A sole author (KF) synthesized input from these interactions to formulate a list of positions. These positions covered three main areas: 1) the impact of an approved anti-amyloid therapy on healthcare systems, including costs, reorganization (logistics) of outpatient services, and system readiness across countries, along with care and diagnostic pathways for patients with suspected AD/cognitive decline; 2) strategies for discussing an anti-amyloid therapy with patients, considering current results, and examining the patient-caregiver perspective to address challenges; 3) the research landscape and priorities in AD following potential approval of an anti-amyloid therapy, encompassing drug development. The formulated positions underwent further scrutiny through an online survey, where participants voted and provided comments. A position was considered adopted if 80% or more of the participants supported it. Positions with support between 50 and 80% underwent revision, while those with less than 50% support were rejected. A second round was conducted for positions that neither gained adoption nor rejection in the first round, requiring an 80% agreement for adoption. If an 80% agreement rate was not reached, the position would be rejected. Human Ethics and Consent to Participate declarations was not applicable.

Results

A total of 24 positions were circulated for the first round of voting of which 22 positions reached the threshold of 80% agreement and 2 reaching the 50% threshold. The latter were rephrased and voted upon again in the second round both reaching the 80% threshold. In total 24 positions were included. For further details on voting, see Supplemental Table S1.

Positions

Section 1: Impact of the approval of an anti-amyloid therapy on health care systems (e.g., costs, reorganization and logistics of outpatient services, system readiness across countries), diagnostic pathways for patients suspected of AD/cognitive decline and clinical care

Given the current state of evidence, removal of amyloid is only clinically relevant in patients who are symptomatic due to AD neuropathology in the MCI or mild dementia stage. Therefore, for treatment with anti-amyloid antibodies to be safely and effectively introduced into clinical practice, a diagnosis of MCI or mild dementia due to AD

and subsequent initiation of anti-amyloid antibody therapy will require a biomarker-based diagnosis. As AD can be conceptualized as a clinic-biological entity, it is important to underline that diagnosis requires the presence of well-defined phenotypes together with the presence of a positivity of pathophysiological biomarkers of AD [9, 10]. Other diagnostic schemes propose different definitions of AD such as a purely biological definition where presence of amyloid deposition in the brain is equated to disease and would open up for treatment in an asymptomatic phase [11]. At present, many patients with AD and other neurodegenerative dementia disorders are diagnosed outside centers with adequate access to biomarker sampling such as cerebrospinal biomarkers and/or amyloid PET imaging [12]. Plasma biomarkers that can rule in or rule out pathological amyloid deposition are being developed [13–15] and may help to curtail this shortcoming. However, plasma biomarkers are yet to be introduced into clinical practice and are unlikely to fully eliminate the need for confirmatory biomarker modalities. Moreover, even with the introduction of plasma biomarkers, interpretation and communication of results will require training and experience [16].

Currently, compounds such as Lecanemab [5]and Donanemab [6] are given via intravenous infusions every 2 or 4 weeks respectively, which in most European countries is likely to be undertaken in specialized settings. Furthermore, today, many patients are not followed up or monitored in a systematic and preplanned manner by physicians or are done so in settings without easy access to dementia specialists [17]. Both monitoring of the long-term effectiveness and of drug-specific side-effects, such as Amyloid-related Imaging abnormalities (ARIA), will require regular clinical assessment and frequent MR scans [18]. Indeed, the EMA has mandated MR scans to be performed before the 5th, 7th and 14 th dosing of Lecanemab. Moreover, data monitoring via registries to address remaining data gaps regarding long-term effectiveness, safety, and cost-effectiveness will also be necessary. Here, the EMA have instructed the sponsor to set up an EU-wide registry study with patients treated with Lecanemab and that a post-authorisation safety study to further characterize ARIA-E and ARIA-H and assess the effectiveness of the risk minimization measures be conducted (https://www.ema.europa.eu/en/medicines/human/EPAR/leqembi.).

There is also a risk of concerned citizens seeking out their primary care physician due to very subtle memory problems, not meeting criteria for MCI, which may threaten to overwhelm expert centers if effective screening methods and triage are not available. This could include basic cognitive tests (perhaps digital cognitive testing done remotely via apps), which should rule out those subjects that do not have relevant cognitive impairment with a high likelihood. In contrary, although concerns of system overload are warranted, the present status is that many patients with AD are never diagnosed or significant delay in diagnosis [19] means that patients are diagnosed late in the disease outside the window for treatment with Lecanemab. This underscores the need for education on early AD in primary care and the provision of care pathways, which support primary care physician in dealing with diagnosis and care of early AD patients.

Disparities regarding access to diagnosis and treatment is a concern. Given the complexity of diagnosis and anti-amyloid antibody treatment both at the level of the health care system and at the individual patient level, these treatments may exacerbate existing inequalities in AD management across regions and healthcare systems, at least in the initial phase of introduction. EADC investigators have previously published estimates on the cost related to the roll-out of Lecanemab [8]. While there is still uncertainty regarding the actual pricing, it highlights that for some healthcare systems medication costs may become an issues. In addition, costs of diagnosis and treatment administration, may be obstacles for access to treatment in some European countries [20]. In addition, disparities in access may be related to geographic differences across Europe and within countries (i.e. distance to specialized center), and to individual patient characteristics (e.g., social, educational or cultural background). Care has to be taken that disparities in health care access do not occur across disease severity (e.g. by a preferential focus on early [vs more severe] disease stages) or across etiologies (e.g. by a disproportionate allocation of funds to detection of AD over other dementia disorders).

Changes to diagnostic and care pathways will be required to accommodate DMTs. Thus, the licensing of DMTs is also an opportunity to rethink other aspects. As an example, the introduction of thrombolysis in acute stroke led to the formation of stroke units bringing a holistic approach to stroke management [21]. Likewise, antibody treatment of AD may lead to developing comprehensive Alzheimer treatment centers with pharmacological and non-pharmacological treatments plus social care and support for patients and their caregivers. Lastly, further training is needed in centers offering anti-amyloid therapies and in relation to other services where patients on treatment may present with ARIA related symptoms, especially in acute settings (e.g., emergency departments and stroke units). As with other initiatives that may aim to ensure patient safety, the EMA have asked the sponsor to provide training on ARIA to centers offering Lecanemab (https://www.ema.europa.eu/en/medicines/human/EPAR/leqembi) (Table 1).

Table 1 Position statements for section 1

• Fundamental changes in care pathways are necessary to ensure delivery of DMTs and to safeguard that patients with other neurodegenerative diseases will receive a timely diagnosis and medical management
• Vigilance with regards to exacerbation of existing or new disparities across countries, regions and patient groups is important and countermeasures should be enacted if they should appear
• Reliable diagnostic procedures at the level of primary care providers are needed to ensure that patients who will benefit from referral to a specialized center are identified. These may include patients with identifiable other causes of cognitive impairment (e.g. depression, vitamin deficiency) or patients with advanced disease (e.g. severe dementia)
• Affordable and reliable diagnostic tools and clinical decision support tools to assist the diagnosis of AD and other neurodegenerative diseases should be developed to help physicians at the level of primary care providers as well as specialist centers
• Whenever anti-amyloid antibodies may be indicated, the diagnosis of AD should be biomarker-based and carried out in centers with access to such biomarkers and with physicians experienced in applying and interpreting biomarkers
• Treatment should be initiated and monitored by physicians with experience in following patients with AD
• Gaps in education and training of staff involved in the biomarker-based diagnosis of AD, and follow-up of patients treated with anti-amyloid antibodies should be identified and educational activities should be offered which could include certification of staff
• Current management approaches such as acetylcholine esterase inhibitors and non-pharmacological treatment should continue to be offered following the introduction of a DMT
• Centers in which anti-amyloid antibody therapy is given should have easy access to MRI scans to evaluate possible ARIA and neuroradiologists trained in recognizing these changes
• Further development of existing MRI protocols to detect and follow ARIA should be undertaken

Section 2 How to discuss an anti-amyloid therapy with patients in light of the current trial results – patient—caregiver perspective – how to meet challenges

It is important to underline that anti-amyloid antibodies target a population of relatively mildly impaired patients with proven underlying Alzheimer´s pathology (mild cognitive impairment and mild dementia stages of AD) which closely resemble the study populations in the pivotal clinical trials of both lecanemab [5], donanemab [6, 22]and aducanumab [4]. This is in line with the language put forth on the intended patient population by the EMA for Lecanemab (https://www.ema.europa.eu/en/medicines/human/EPAR/leqembi). The vast majority will be community-dwelling and despite cognitive impairment have retained capacity to make informed decisions about undergoing monoclonal anti-amyloid antibody therapy. Patients should be advised to involve caregivers, but the main emphasis is on informing the patient and respecting the autonomy of the patient to decide on treatment in the form of shared decision-making. Managing expectations for patients not eligible for anti-amyloid therapy as well as for patients who may qualify for anti-amyloid treatment will be necessary and will require skills, time, and information material. Practical aspects of regular visits to hospitals every 2 to 4 weeks for infusion and undergoing frequent MRI scanning need to be communicated as this may be burdensome to patients and create other issues of concern, e.g., perhaps excluding thrombolysis in the case of a stroke and how to include MRI scanning into the clinical work-up of a suspected emerging stroke. Communicating long-term treatment effects in terms of a slowing of disease progression instead of stopping progression, will create challenges. Time to event which could be progression from one clinical stage to the next, or time saved may help to explain the impact of therapy in the context of an elderly population. Several factors modulate efficacy and safety of the treatment such as sex, age, tau burden, co-morbidities and an APOE-epsilon 4 carriership [23]. To inform about their impact on treatment response and risk adds to the complexity. As EMA in their positive opinion regarding Lecanemab have stipulated that patients who are homozygous for APOE-epsilon 4 are not eligible for treatment, testing for APOE genotype will be mandatory. Thus, detailed verbal, and written information on the medical and psychosocial implications on disclosing APOE genotype results needs to be available to the patient to facilitate decision making and risk communication. Of special ethical consideration is to inform patients that both disclosure and non-disclosure of their genetic status may create concern in their offspring.

It is currently unclear if stopping treatment when patients convert to amyloid-negative on visual read of scans (i.e., amyloid levels on PET imaging below what is observed in cognitively unimpaired persons termed "Treatment-related amyloid clearance") is feasible and may be done without change in future progression rate. Also, a monthly maintenance dosing schedule (instead of bi-weekly) after 18 months has been proposed for lecanemab for the US and maybe also apply for the European Union in case of approval. Generally, it is also important to discuss that uncertainty remains in terms of treatment effects beyond 18 months [5, 6]. Finally, patients are likely to experience progression on treatment

Table 2 Position statements for section 2

• Shared decision making should be the basis for discussions of therapy and decisions on whether a patient is eligible to receive a DMT
• Discussing with the patient whether family members or other persons should be involved in the decision process may be considered
• Balanced information about possible benefits and harms should be given including alternatives to start of anti-amyloid antibody treatment
• Communicating that progression will occur on treatment albeit at a slower rate should be done before start of treatment
• Events which may lead to treatment being stopped should be addressed such as the appearance of side-effects that give safety concerns or are unacceptable to the patient
• Stopping criteria should be developed which may include conversion to amyloid negativity or progression to moderate or severe dementia
• Personalized estimates of risks and benefits should be given when possible
• Both verbal and written information should be made available to the patient with regards to anti-amyloid antibody therapy

to moderate and eventually severe stages of the disease. It may therefore also be pertinent early on to discuss that the risk/benefit relation of the treatment will change over time Table 2.

Section 3: The research landscape and priorities within research in AD following a possible approval of an anti-amyloid therapy including drug development (in the later stages and as regards other modes of action)

The findings from recent studies of anti-amyloid antibodies [5, 6, 22, 24–26] represent an inflection point in translating the understanding of AD pathophysiology to clinical practice. These studies show that amyloid is a key player in the disease´s progression with relevance to pharmacological targets and strengthens the amyloid cascade hypothesis albeit in a revised form extending to other pathophysiological processes. There is now compelling evidence linking a significant reduction of brain amyloid to the efficacy of anti-amyloid antibodies in the initial stages of AD [5, 6]. These breakthroughs have furthered our understanding of AD. There is good scientific evidence to suggest that the clinical effects of anti-amyloid antibodies are mediated through amyloid plaque removal, e.g. correlative analyses of clinical trial data [27, 28], and mechanistic data summarizing the refined amyloid cascade hypothesis [29, 30]. The strongest evidence for amyloid removal as surrogate outcome comes from aggregated clinical trial data and it would be premature to use amyloid lowering as the only primary endpoint for clinical trials in early AD nor as a surrogate marker in clinical praxis. Individual patient correlations should be demonstrated instead. There is an ongoing debate about the clinical relevance of the effect sizes of these drugs [31–34]. In the opinion of the authors of this paper, there are clear arguments to conclude that the effects are clinically meaningful. Furthermore, the risk/benefit ratio can be improved by restricting the eligible treatment population to non APOE4-homozygotes, which is the basis of the label in the UK and will most likely be included in the EMA label. Thus, the EADC endorses the clinical use of monoclonal anti-amyloid antibodies as an important part of the therapeutic regime in carefully selected patients with early AD. If a larger effect size is to be achieved e.g., such as halting a disease in the earlier stages, combination strategies targeting more than one pathway are most likely needed. Meaningful improvements are likely to come gradually through ongoing refinement of molecular strategies, better patient selection, and the use of combination therapies [35]. The data of the two most recent clinical trials on Lecanemab [5, 24] have with the decision by the EMA been shown to meet the evidence standards set by European regulators for drug approval (approximately 30% difference in favour of Lecanamab over placebo on the primary endpoint over 18 months). However, several important questions remain open. This includes the benefits of treatment beyond 18 months [5, 6](especially taking into consideration the long duration of AD), data on long-term safety and the need for MRI monitoring, and the effects of discontinuing or pausing treatment, although data from the TRAILBLAZER-ALZ II trial suggests that this is feasible without compromising treatment effect in the short term [6]. Experience from other diseases might offer insights into how these evidence gaps may be bridged. For instance, the introduction of effective DMTs for multiple sclerosis (MS) led to the creation of an international registry, MSBase (https://www.msbase.org/.), which is partly sponsored by an industrial consortium for long-term data collection and harmonization. Yet, there are distinctions between MS and AD, particularly concerning disease prevalence and patient follow-up. AD patients' follow-up is not limited to specialists as is the case for many MS patients who often receive care in hospitals or from private neurologists. Current pharmacological treatment of AD is often delivered by primary care physicians, but with the introduction of antibodies, diagnosis and follow-up for AD patients must be provided with similar expertise to what is seen in MS. At present, only a few

Table 3 Position statements for section 3

• Continued research and development of compounds for the treatment of AD with other mechanisms of action is required
• Amyloid antibodies are likely in due course to become the standard of care for eligible patients in the early stages of AD in Europe. This should not preclude the possibility of offering placebo-controlled trials to explore other treatment approaches
• Presently, amyloid lowering is not sufficiently supported by evidence to be considered a surrogate measure of clinical efficacy
• The field should prepare for the introduction of combination therapy (beyond choline-esterase inhibitors). More effective therapy is needed, and this is most likely going to necessitate combination therapy
• Sponsors are encouraged to share data from drug trials of anti-amyloid antibodies with academic centers to generate knowledge on e.g., responders versus non-responders and who are at a high versus low risk of side-effects
• Continued long-term data collection and continued follow-up of patients treated with anti-amyloid therapies is needed to assess safety and effectiveness in a real-world setting through a combination of phase-4 post approval studies and European registries

European countries have dementia registries with longitudinal data covering a representative proportion of patients diagnosed with AD and other dementia disorders [36]. Global diabetes registries might offer an even closer parallel [37] as diabetes is often diagnosed and managed in primary care. There are research questions relating to specific subgroups of patients which may only be answered in placebo-controlled trials. This covers patients not included in the pivotal phase 3 studies (e.g., patients outside the age range) or patients with e.g., Downs syndrome. The implementation of anti-amyloid antibody as a standard treatment might be limited by factors such as drug costs and reimbursement conditions, diagnostic limitations, potential contraindications, and an expected staggered rollout across various regions. Furthermore, side effects, notably ARIA observed in antibodies associated with prominent amyloid reduction [38–40] and linked to severe outcomes, including fatalities [41], may dissuade certain patients from opting for the treatment after carefully evaluating the risks and benefits. Hence, irrespective of the decision from regulatory bodies, it is imperative to continue research on these specific antibodies under evaluation in Europe, such as to personalize their use, and to explore new compounds with alternative mechanisms of action (Table 3).

Conclusion

The approval of anti-amyloid antibodies for early AD in European countries heralds a new era of drug treatment for AD. This paradigm shift necessitates fundamental changes to the health care systems across Europe with respect to how AD patients are identified, diagnosed, managed and followed up. These changes will also benefit patients who may not be eligible for treatment as an earlier diagnosis carries benefit regardless of whether anti-amyloid antibodies are indicated. It is imperative to understand that anti-amyloid antibodies open a "window of opportunity" for AD patients that meet indications in order to communicate the treatment benefits and limitations of these therapies clearly to patients and the public. A comprehensive and realistic assessment of treatment risks and benefits will significantly influence their successful implementation and eventually make them the new standard of care for a specific population of AD patients at the early stage of disease over a relevant period of time. Concurrently, it is crucial to ensure the delivery of high-quality health care to all patients with cognitive disorders. Numerous statements and recommendations have been formulated to offer guidance in this endeavor. However, this guidance must be informed by evidence to be acquired. Regulatory authorities and health technology assessment bodies in Europe will soon make decisions regarding approval and reimbursement conditions of the first among a series of new drugs. Additional disease modifying drugs with alternative mechanisms of action and route of administration will be developed in the near future. Furthermore, dynamic advances in biomarkers and changes to health care systems will continue to evolve. Thus, the content of this paper will necessitate periodic updates to remain current and relevant in light of these ongoing developments which may have more focus on the directions research may take in the future.

Supplementary Information

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Supplementary Material 1.

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FJ serves on an advisory boards, participated in educational and speaker activities for Abbvie, Eisai, Eli Lilly, GE Healthcare, Grifols, Janssen Cilag, Novonordisk, Roche, and serves on a data monitoring committee for AC Immune.
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Authors' contributions
KF came up with the idea for the study, KF and LF designed the study, all authors contributed to data collection, all authors contributed to the execution of the study, KF and LF drafted the initial version of the manuscript, all authors provided input to the manuscript, all authors approved the final manuscript.

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