

# Léčba demence

**Prof. MUDr. Jakub Hort, Ph.D.**

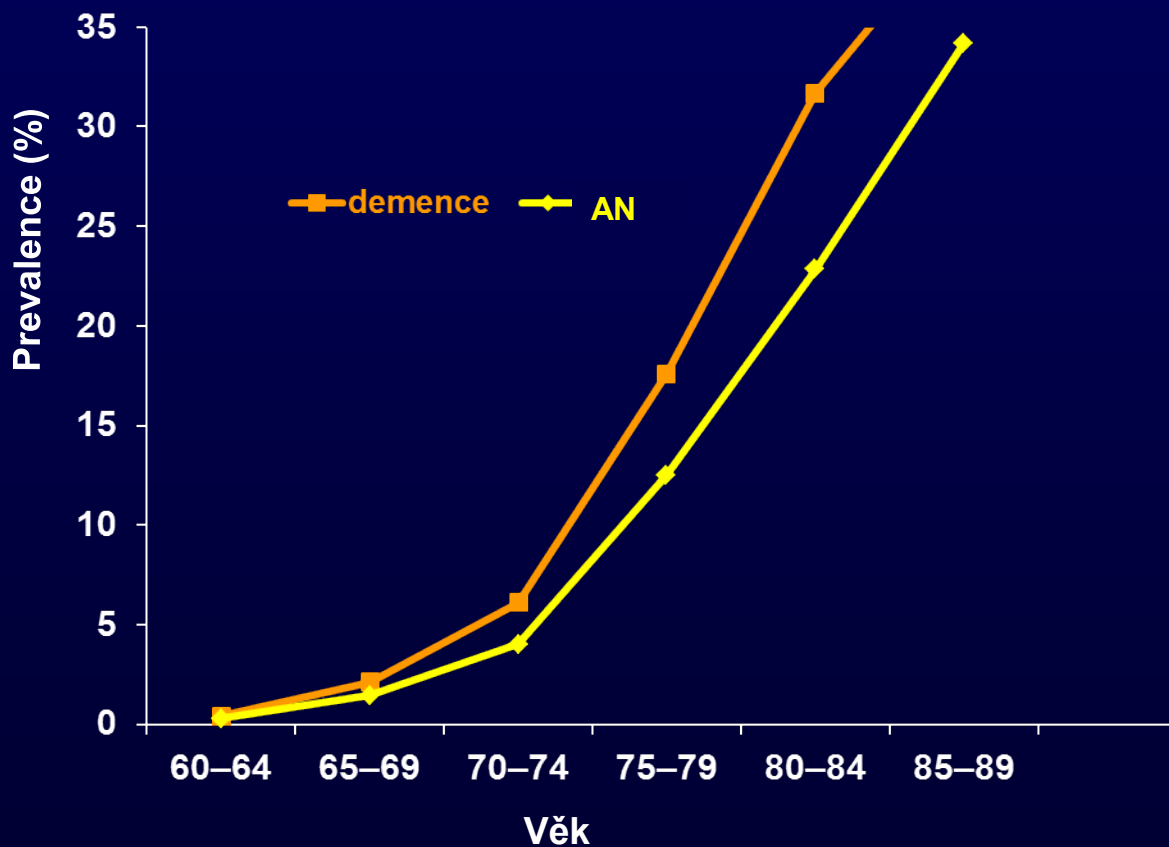
**Neurologická klinika UK, 2. LF a FN Motol**



# ČR – senioři - střední predikce

- 2050 – 10.75 mil obyvatel
  - 10 mil
  - 11.25 mil
- Počet lidí nad 65 let se zvýší ve všech 3 predikcích
- Střední predikce:
  - 2,240,000 (2024)...2,475,000 (2035)...3,100,000 ( 2050)
  - **v 2050 tedy o 860 tis seniorů nad 65 let více!**

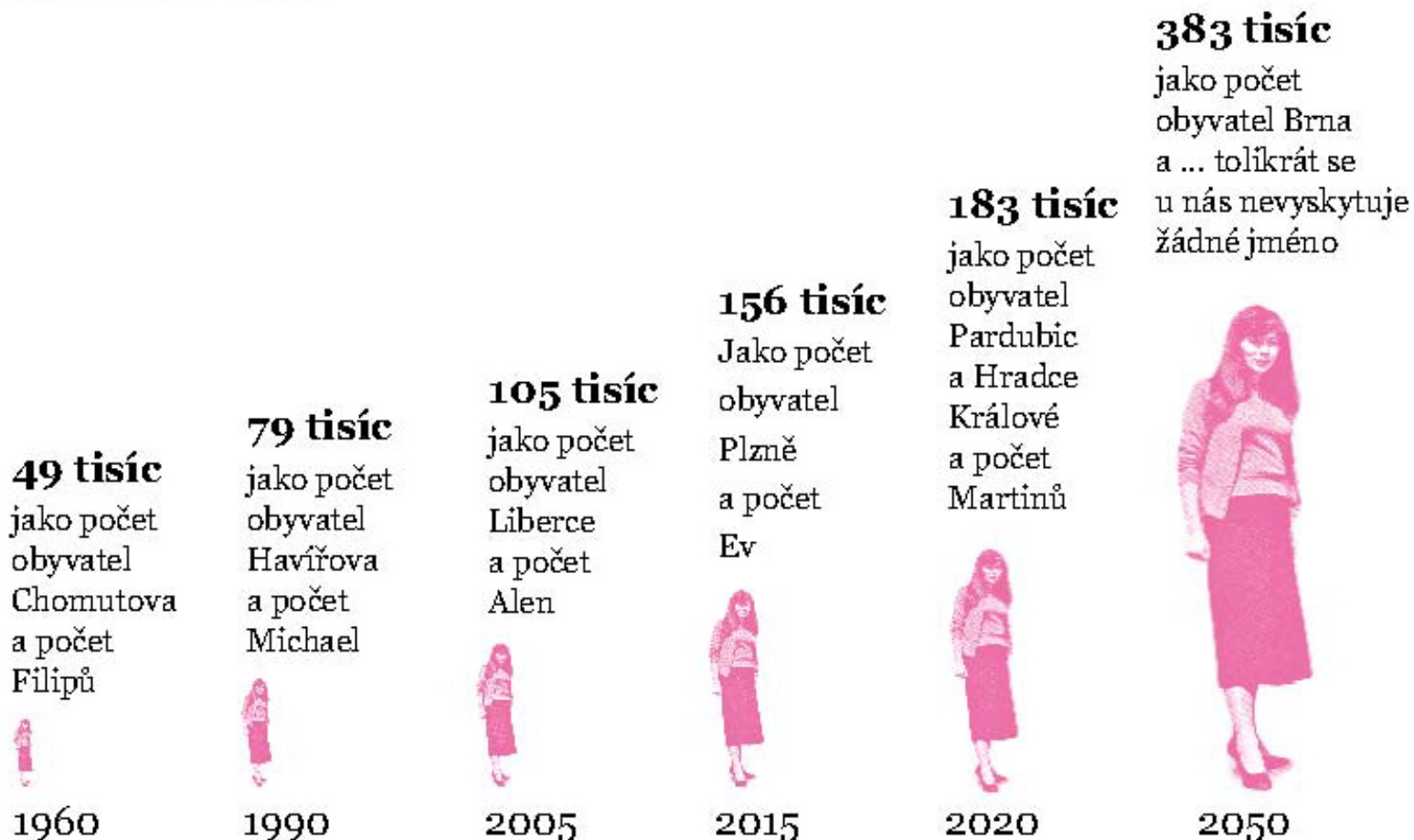
# Věk – rizikový faktor AN



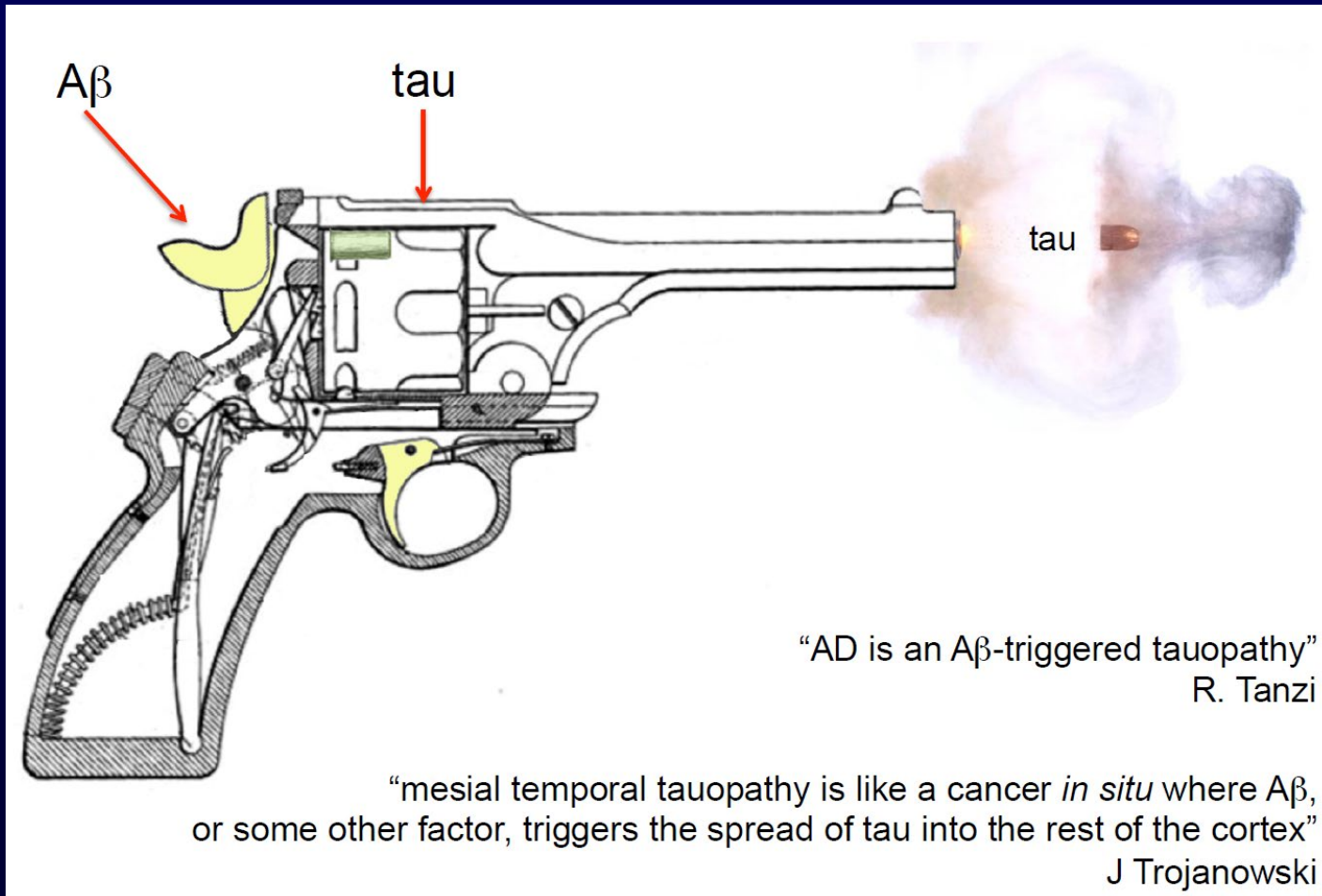
## Demence včera, dnes a zítra

### Predikce vývoje počtu lidí s demencí v ČR

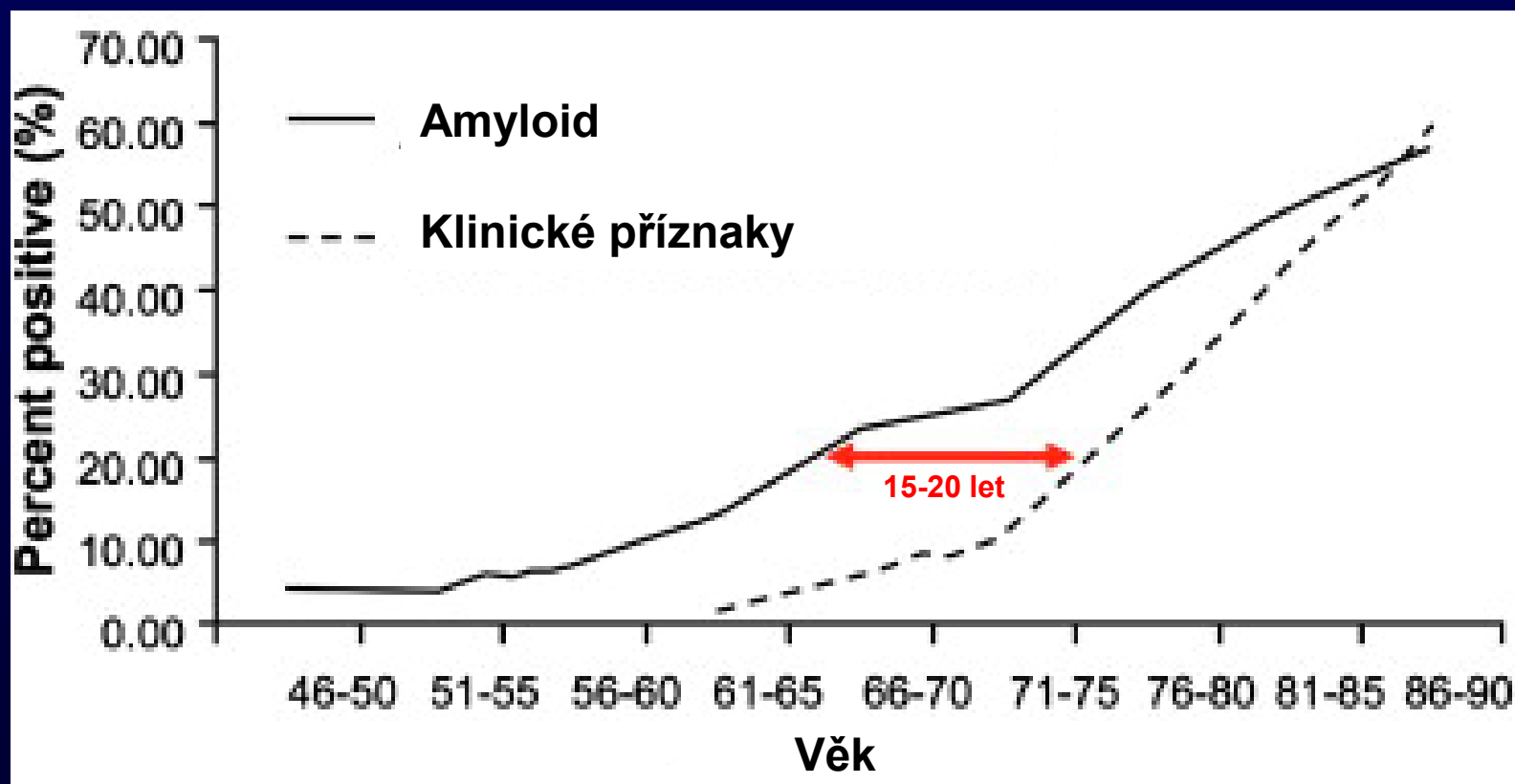
Zdroj: vlastní výpočty



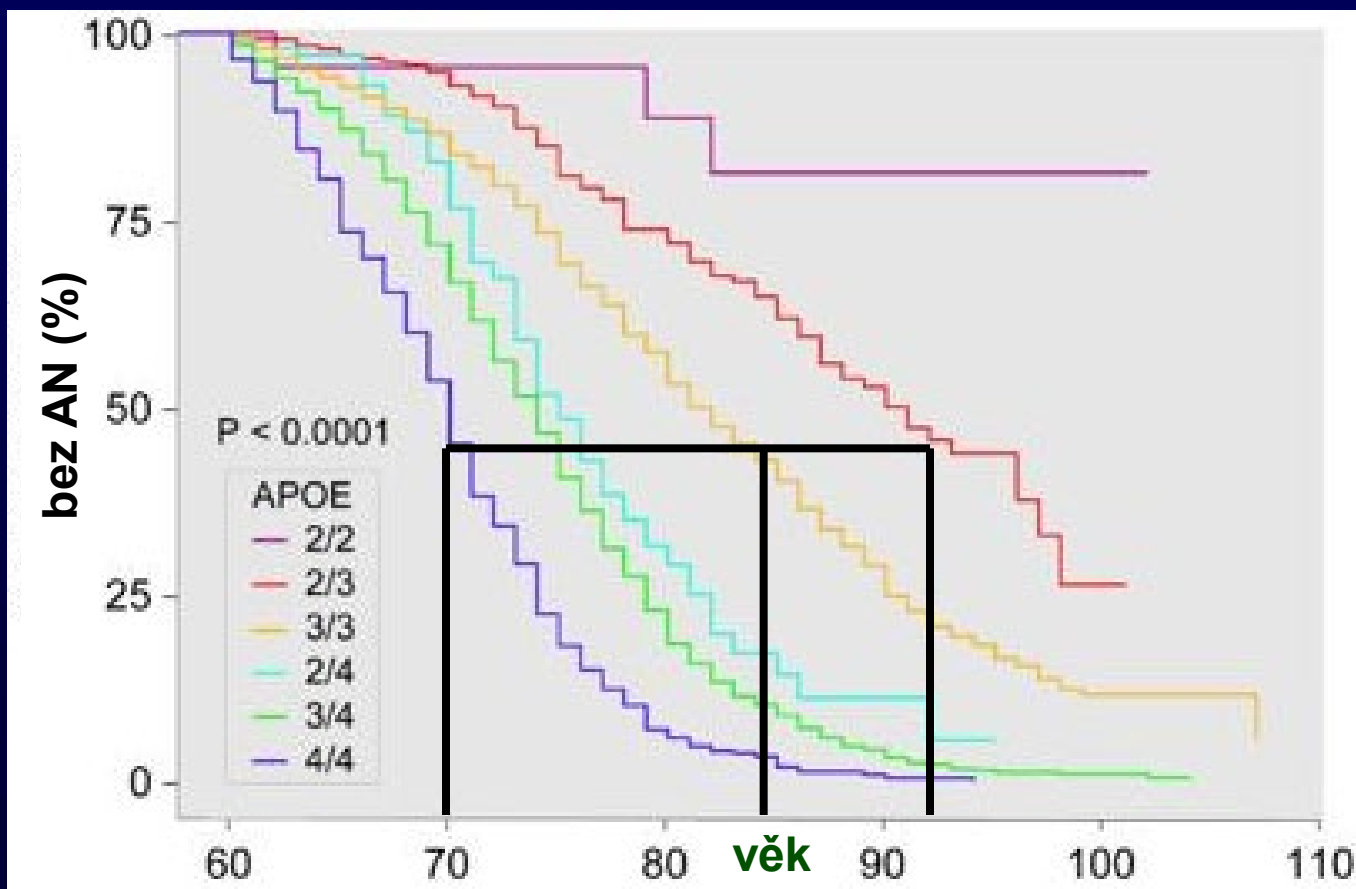
# Tau nebo amyloid A $\beta$ ?



# Nejdřív amyloid a až pak příznaky



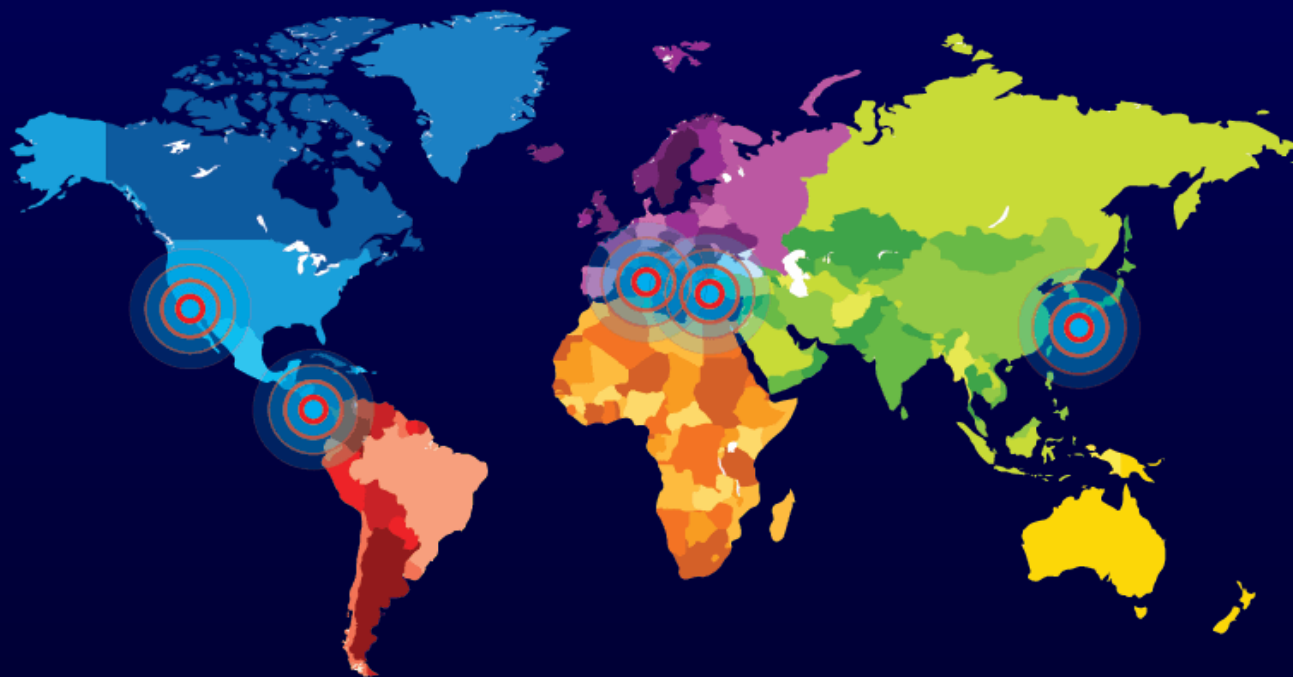
# ApoE $\epsilon$ 4 ovlivňuje věk nástupu AN



- Gen pro ApoE:  $\epsilon$ 2 (8%),  $\epsilon$ 3 (78%), heterozygoti  $\epsilon$ 4 (14-16%), homozygoti  $\epsilon$ 4 (1%)
- 2-3x vyšší riziko heterozygotů, 11-12 x u homozygotů  $\epsilon$ 4

# Modré zóny

- Dlouhověkost
- Pohyb, střídmost, purpose of life



- Rovněž vyspělé země: demence o 10- 20% méně – prevence

# Metaanalýza na prevenci AN

Cognitive neurology

 OPEN ACCESS

REVIEW

## Evidence-based prevention of Alzheimer's disease: systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials

Jin-Tai Yu <sup>1</sup>, Wei Xu <sup>2</sup>, Chen-Chen Tan,<sup>2</sup> Sandrine Andrieu,<sup>3</sup> John Suckling,<sup>4</sup> Evangelos Evangelou,<sup>5</sup> An Pan,<sup>6</sup> Can Zhang,<sup>7</sup> Jianping Jia,<sup>8</sup> Lei Feng,<sup>9</sup> Ee-Heok Kua,<sup>9</sup> Yan-Jiang Wang,<sup>10</sup> Hui-Fu Wang,<sup>2</sup> Meng-Shan Tan,<sup>2</sup> Jie-Qiong Li,<sup>2</sup> Xiao-He Hou,<sup>2</sup> Yu Wan,<sup>2</sup> Lin Tan,<sup>2</sup> Vincent Mok,<sup>11</sup> Lan Tan,<sup>2</sup> Qiang Dong,<sup>1</sup> Jacques Touchon,<sup>12</sup> Serge Gauthier,<sup>13</sup> Paul S Aisen,<sup>14</sup> Bruno Vellas<sup>15</sup>

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For numbered affiliations see end of article.

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**ABSTRACT**  
**Background** Evidence on preventing Alzheimer's disease (AD) is challenging to interpret due to varying study designs with heterogeneous endpoints and credibility. We completed a systematic review and meta-analysis of current evidence with prospective designs to propose evidence-based suggestions on AD prevention.  
**Methods** Electronic databases and relevant websites were searched from inception to 1 March 2019. Both observational prospective studies (OPs) and randomised controlled trials (RCTs) were included. The multivariable-adjusted effect estimates were pooled by random-effects models, with credibility assessment according to its risk of bias, inconsistency and imprecision. Levels of evidence and classes of suggestions were summarised.  
**Results** A total of 44 676 reports were identified, and 243 OPs and 153 RCTs were eligible for analysis after exclusion based on pre-decided criteria, from which 104 modifiable factors and 11 interventions were included in the meta-analyses. Twenty-one suggestions are proposed based on the consolidated evidence, with Class I suggestions targeting 19 factors: 10 with Level A strong evidence (education, cognitive activity, high body mass index in late life, hyperhomocysteinaemia, depression, stress, diabetes, head trauma, hypertension in midlife and orthostatic hypotension) and 9 with Level

The past few decades have witnessed great global efforts in updating and upgrading the evidence on how to prevent Alzheimer's disease (AD),<sup>5 6</sup> accounting for approximately two-thirds of all cases of dementia and affecting up to 20% of individuals older than 80 years.<sup>7 8</sup> Nevertheless, key issues in the field are the inconsistency among conclusions and variable levels of credibility arising from the wide variety of study designs.<sup>9</sup> Two types of studies are generally regarded as having the greatest impact on the extant literature: (1) observational prospective studies (OPs), which describe temporal relationships with potential causal links and often use large samples recruited from community dwellers; and (2) randomised controlled trials (RCTs), which possess strong internal validity to infer causality by testing the effects of specific interventions on the incidence of AD. Although both approaches are useful, the major concerns in OPs are usually the elusive sources of bias when interpreting the identified wide-ranging factors, and current RCTs are often compromised by short follow-up durations, subjective endpoints, small sample sizes and specific recruitment criteria with uncertain generalisability.<sup>5</sup> Considerable evidence has been generated regarding AD through OPs and RCTs. Because it is

J Neurol Neurosurg Psychiatry: first published as 10.1136/jnnp-2019-321913 on 20 July 2020. Downloaded from <http://jnnp.bmj.com/> by guest on 01 August 2020.

21 doporučení na 19 faktorů

Yu et al., 2020

# Evidence based

- **10 Level A = silné důkazy**
  - vzdělání, kognitivní aktivity
  - ↑ BMI ve vyšším věku, DM, ↑ homocystein, stres, deprese
  - úrazy hlavy, midlife hypertenze, ortostatická hypotenze
- **9 Level B = slabší důkazy**
  - fyzická aktivita, spánek, vitamin C,
  - obezita ve středním věku, zhubnutí ve vyšším věku, frailty, cerebrovaskulární rizika, fibrilace síní, kouření
- **2 intervence jsou NEdoporučeny**
  - estrogeny (Level A2), inhibitory cholinesterázy (Level B)

# Životní styl – prevence demence

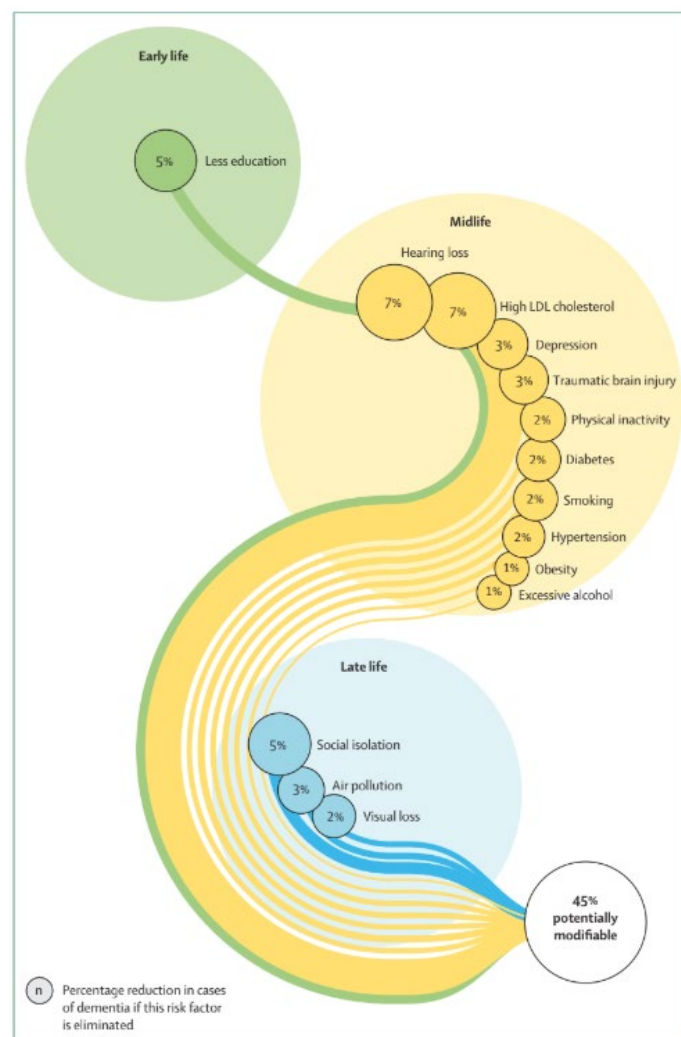
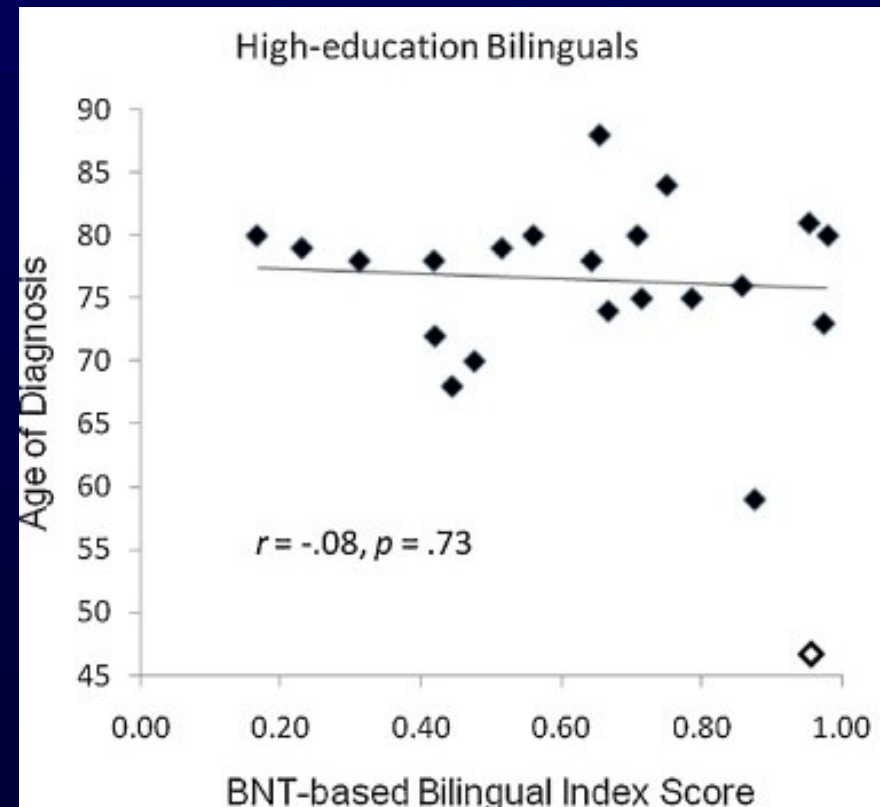
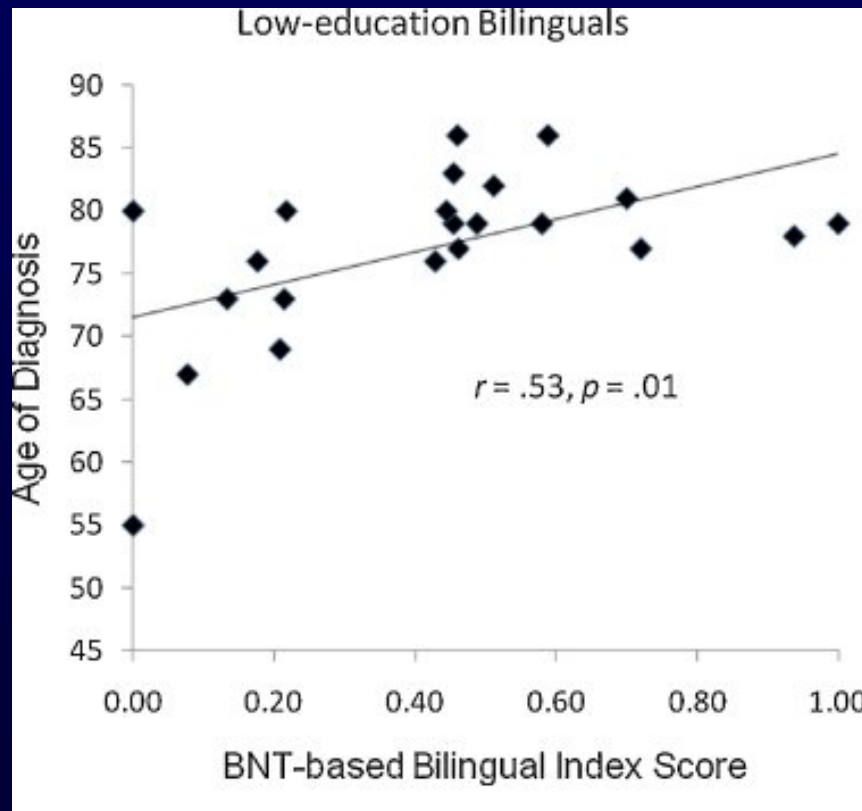


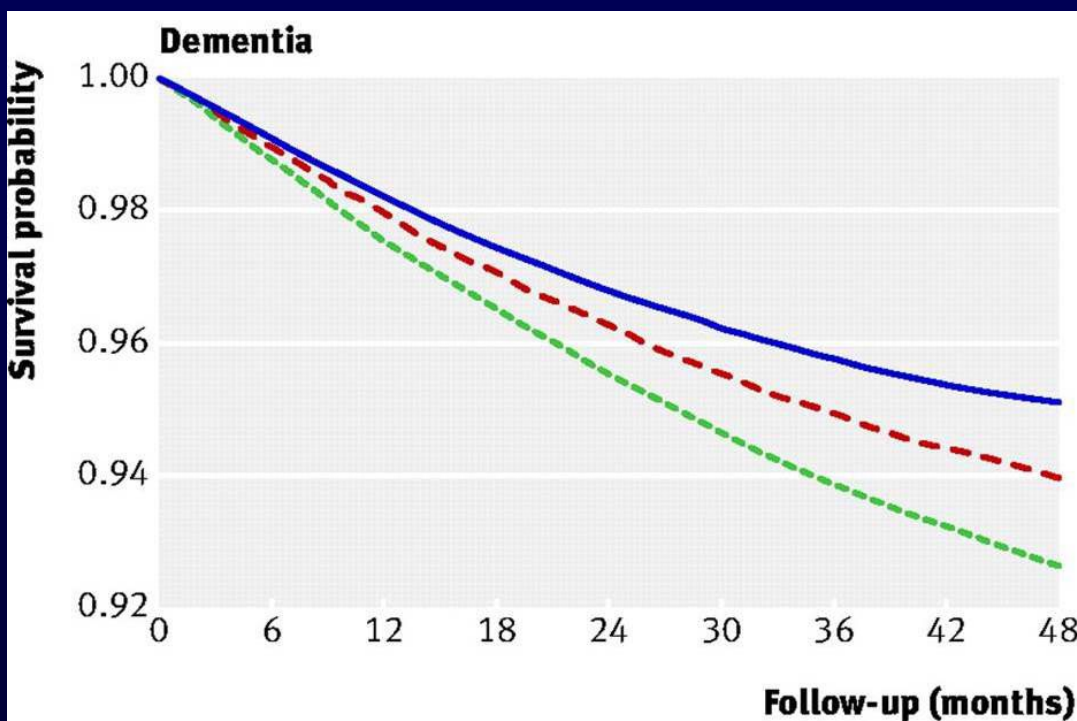
Figure 9: Population attributable fraction of potentially modifiable risk factors for dementia

# Jak být efektivní? - bilingualism

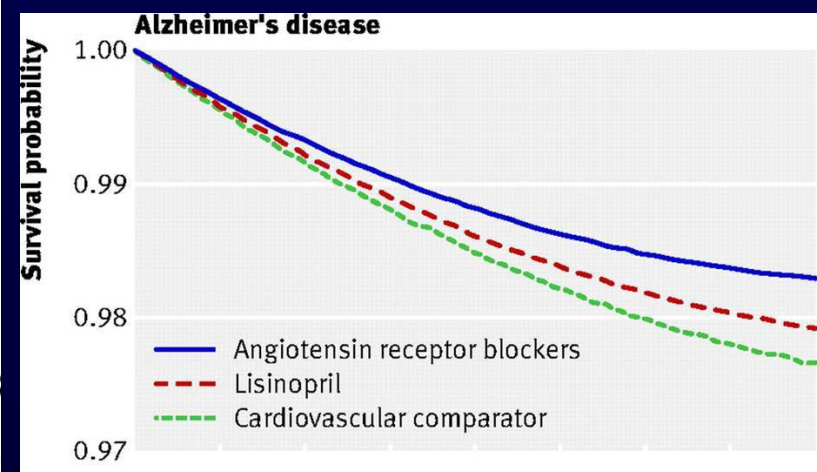
Horní ochranný limit kogn. res.



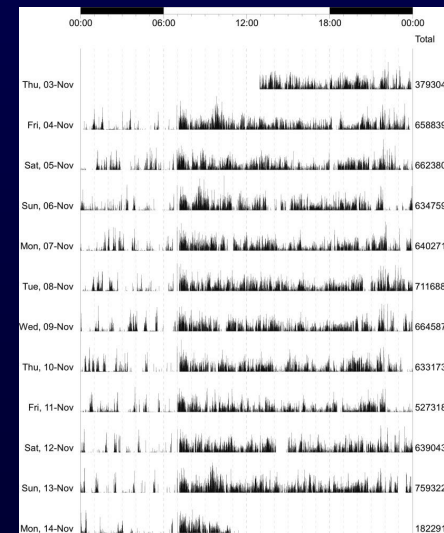
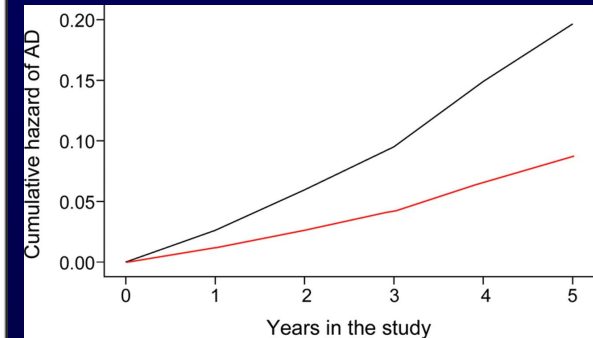
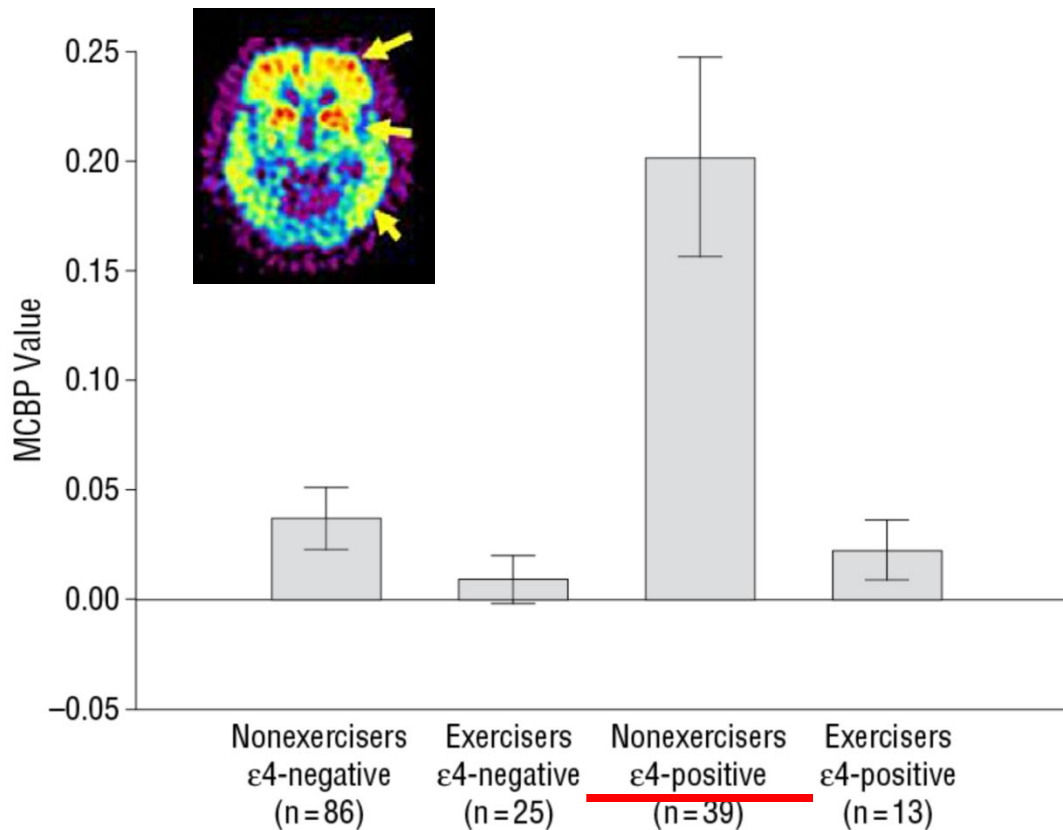
# Jak být efektivní? - hypertenze



816 tis veteránů, 4 roky



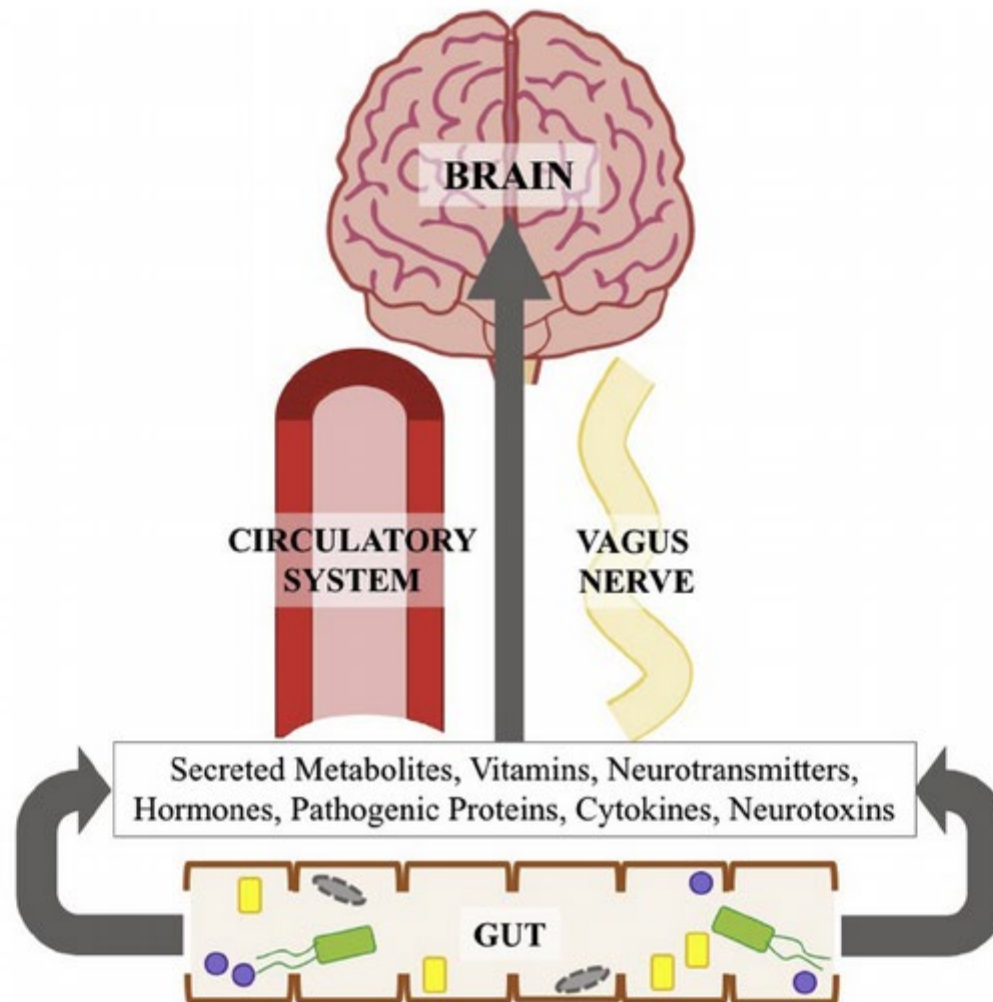
# Jak být efektivní? Fyzická aktivita



# Střevní mikrobiota a AN

*L.J. Spielman et al.*

Neurochemistry International 120 (2018) 149–163



# Screening a prevence

- Mobilní aplikace Terrapino – [www.terrapino.com](http://www.terrapino.com)

The advertisement features a central smartphone displaying the Terrapino app interface. The app's header includes the Terrapino logo (a turtle) and the text "DIGI@MED Award". The main title on the app screen is "Zdravé stárnutí bez Alzheimerova nemoci". Below this, there is a section for "Zjistěte riziko onemocnění" (Find out the risk of disease) with a parrot icon and a "Začít" (Start) button. The app also shows progress indicators for "Dotazníky" (0/8) and "Trénujte mozek" (3/6). A "Dnešní kroky" (Today's steps) section shows a goal of 10,000 steps with a current count of 205. Two QR codes are positioned at the bottom left and right, leading to the app's download page. The bottom of the advertisement includes the Google Play and App Store logos.

**Zdravé stárnutí  
bez Alzheimerova nemoci**

**ZDARMA**  
ke stažení na:

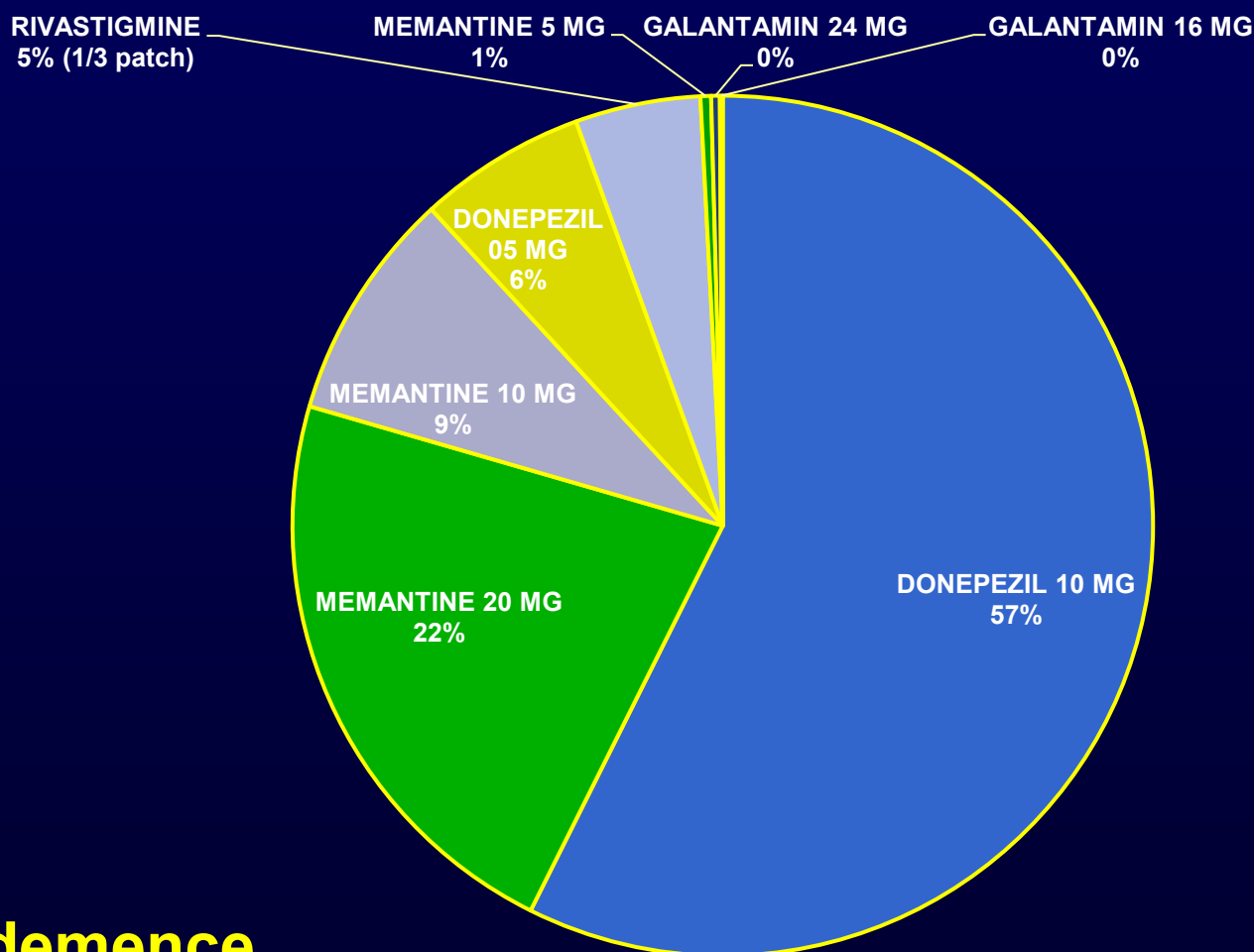
**Google Play**

**Download on the  
App Store**

# Léčba rozvinuté demence u ACH

- Nejlepší výsledky - inhibitory acetylcholinesterázy  
(donepezil - Aricept, rivastigmin - Exelon, galantamin- Reminyl)
- memantine (Ebixa)
- EGb 761
- Tato léčba:
  - 1/dokáže oddálit nejzávažnější stadia onemocnění
  - 2/ oddálit umístění do ústavu
  - 3/ snížit zátěž pečovatелů
  - 4/ zlepšit paměť, zlepšit poruchy chování

# Kognitiva 2023

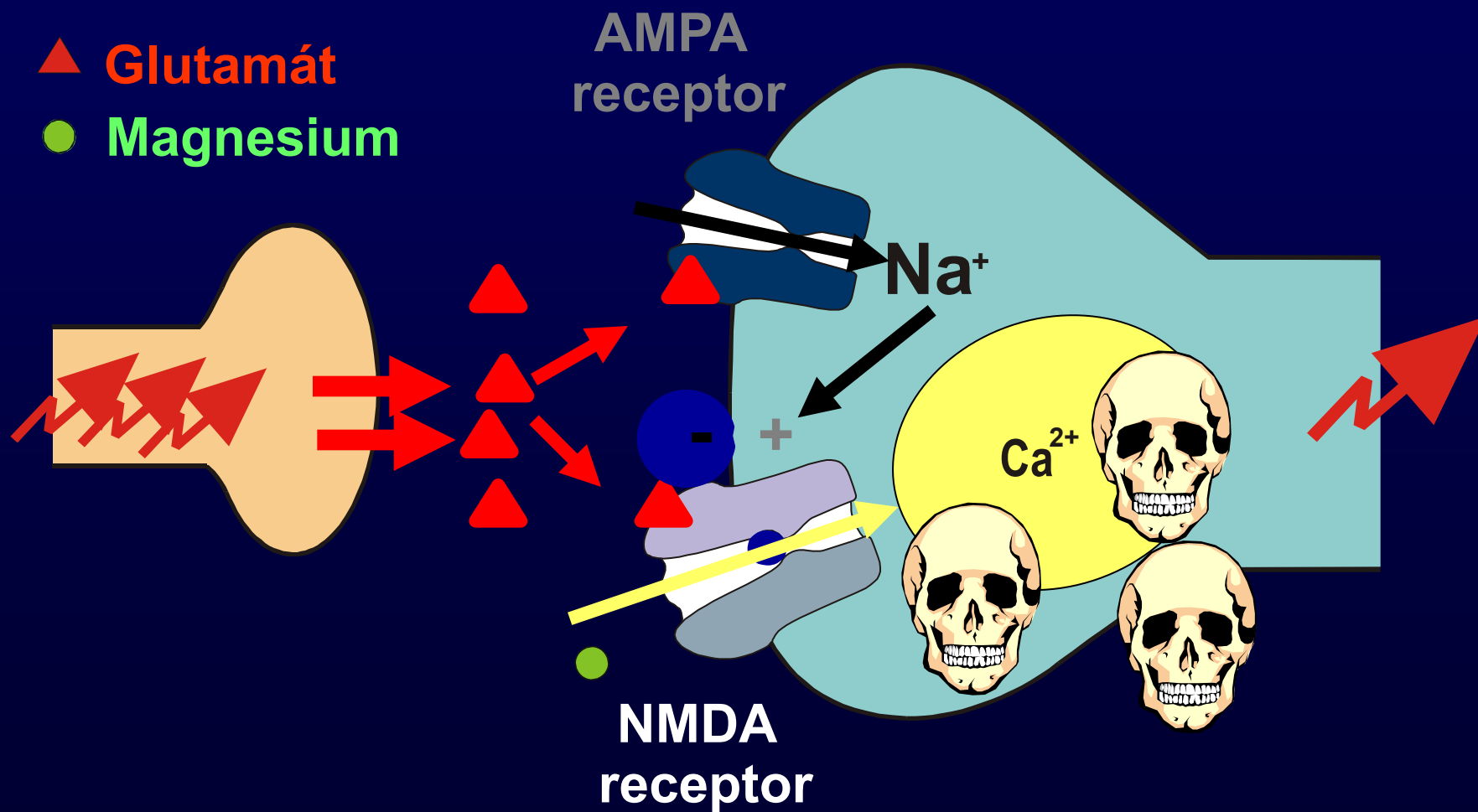


Léčba demence

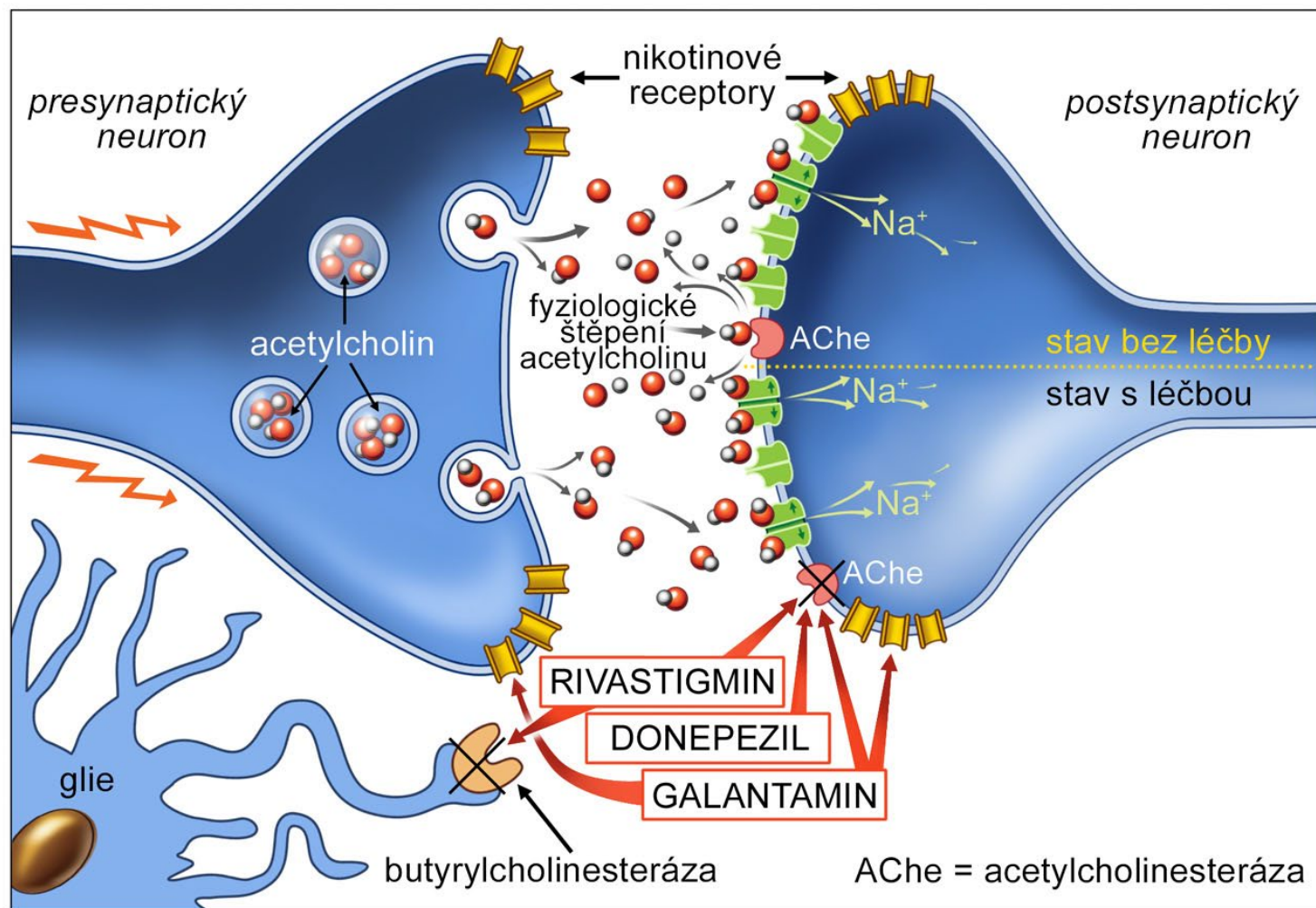
**311 mil Kč**

Zdroj IQVIA YTD12/2023

# Mechanismus účinku memantinu

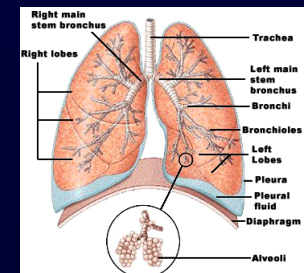
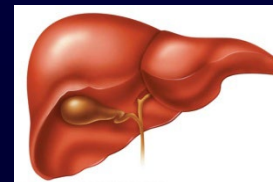
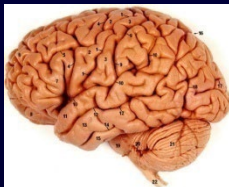
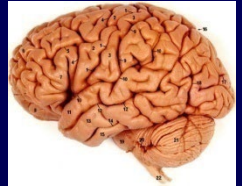


# Inhibitory acetylcholinesterázy



# Inhibitory acetylcholinesterázy

- **acetylcholinesteráza** (mozek - neurotransmise) – donepezil, galantamin, rivastigmin
- **butyrylcholinesteráza** (mozek – zánět, neurodegenerace) rivastigmin



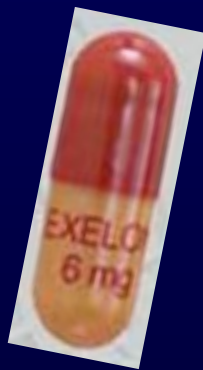
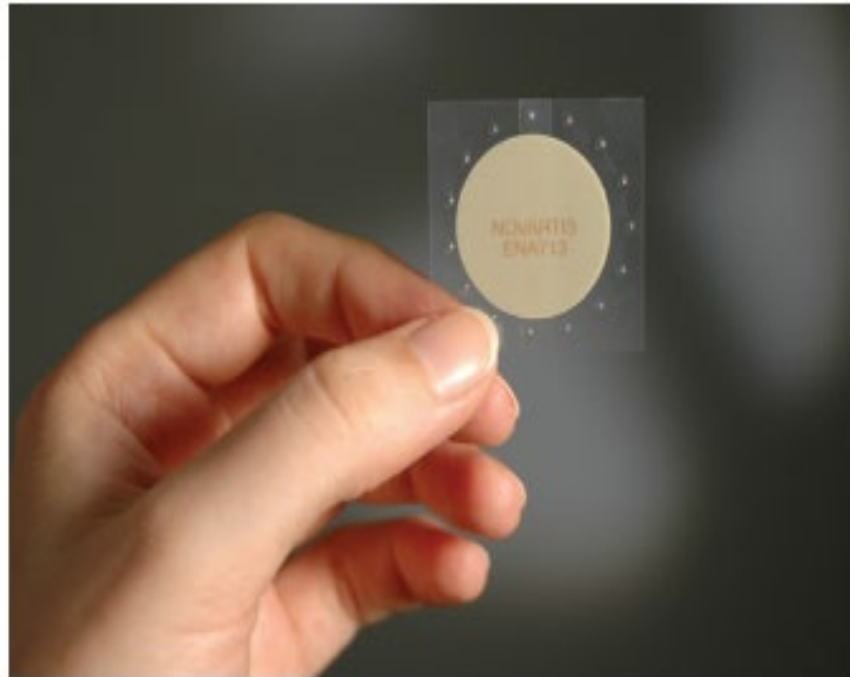


**Figure 1**

A rivastigmine patch



# Inhibitory acetylcholinesterázy u VaD

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7. Data on file (28) - Pfizer Inc.
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# Inhibitory acetylcholinesterázy- LBD

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# Dávkování co nejvýš x než účinky

- **Donepezil** tbl, nebo suspense
  - začínáme 5 mg ( může být již účinná dávka) večer!
  - 10 mg (23 mg USA, testují se náplasti)
- **Rivastigmin** tbl, náplasti
  - 2x1.5 mg 2-4 týdny ( 6 týdnů), 2x3mg, 2x4.5mg, 2x6 mg
  - 4.6 mg, 9.5 mg, 13,3 mg (zvýšená úhrada! Nebo doplatek)
- **Galantamin** 8 mg, 16 mg, 24 mg (2x nebo 1x denně)
- **Memantin** tbl, gtt - 5mg-10-15-20mg nebo 10...20..ráno!

## **EFNS-ENS/EAN Guideline on concomitant use of cholinesterase inhibitors and memantine in moderate to severe Alzheimer's disease.**

Schmidt R<sup>1</sup>, Hofer E, Bouwman FH, Buerger K, Cordonnier C, Fladby T, Galimberti D, Georges J, Heneka MT, Hort J, Laczó J, Molinuevo JL, O'Brien JT, Religa D, Scheltens P, Schott JM, Sorbi S.

### **Author information**

### **Abstract**

**BACKGROUND AND PURPOSE:** Previous studies have indicated clinical benefits of a combination of cholinesterase inhibitors (ChEI) and memantine over ChEI monotherapy in Alzheimer's disease (AD). Our objective was the development of guidelines on the question of whether combined ChEI/memantine treatment rather than ChEI alone should be used in patients with moderate to severe AD to improve global clinical impression (GCI), cognition, behaviour and activities of daily living (ADL).

**METHODS:** A systematic review and meta-analysis of randomized controlled trials based on a literature search in ALOIS, the register of the Cochrane Dementia and Cognitive Improvement Group, was carried out with subsequent guideline development according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

**RESULTS:** Pooled data from four trials including 1549 AD patients in the moderate to severe disease stage demonstrated significant beneficial effects of combination therapy compared to ChEI monotherapy for GCI [standardized mean difference (SMD) -0.20; 95% confidence interval (CI) -0.31; -0.09], cognitive functioning (SMD -0.27, 95% CI -0.37; -0.17) and behaviour (SMD -0.19; 95% CI -0.31; -0.07). The quality of evidence was high for behaviour, moderate for cognitive function and GCI and low for ADL. Agreement of panellists was reached after the second round of the consensus finding procedure. The desirable effects of combined ChEI and memantine treatment were considered to outweigh undesirable effects. The evidence was weak for cognition, GCI and ADL so that the general recommendation for using combination therapy was weak.

**CONCLUSIONS:** We suggest the use of a combination of ChEI plus memantine rather than ChEI alone in patients with moderate to severe AD. The strength of this recommendation is weak.

# Monoterapie nebo kombinace?

Author:  
Date: 2011  
Question: Should AChEI + memantine vs AChEI monotherapy be used for moderate to severe AD?  
Settings:  
Bibliography:

| Quality assessment                                                                                  |                   |                         |                          |                         |                             |                      | No of patients    |                   | Effect                                |                                            | Quality       | Importance |
|-----------------------------------------------------------------------------------------------------|-------------------|-------------------------|--------------------------|-------------------------|-----------------------------|----------------------|-------------------|-------------------|---------------------------------------|--------------------------------------------|---------------|------------|
| No of studies                                                                                       | Design            | Risk of bias            | Inconsistency            | Indirectness            | Imprecision                 | Other considerations | AChEI + memantine | AChEI monotherapy | Relative (95% CI)                     | Absolute                                   |               |            |
| Activities of daily living (follow-up 24 -30 weeks <sup>1</sup> ; Better indicated by lower values) |                   |                         |                          |                         |                             |                      |                   |                   |                                       |                                            |               |            |
| 4                                                                                                   | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious <sup>2,3</sup> | none                 | 728               | 713               | -                                     | SMD 0.08 lower (0.18 lower to 0.02 higher) | ⊕⊕⊕⊕ LOW      | CRITICAL   |
| Behaviour (follow-up 24-30 weeks <sup>1</sup> ; Better indicated by lower values)                   |                   |                         |                          |                         |                             |                      |                   |                   |                                       |                                            |               |            |
| 4                                                                                                   | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision      | none                 | 710               | 698               | -                                     | SMD 0.19 lower (0.31 to 0.07 lower)        | ⊕⊕⊕⊕ HIGH     | CRITICAL   |
| Cognitive functioning (follow-up 24-30 weeks <sup>1</sup> ; Better indicated by lower values)       |                   |                         |                          |                         |                             |                      |                   |                   |                                       |                                            |               |            |
| 4                                                                                                   | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious <sup>3</sup>        | none                 | 726               | 709               | -                                     | SMD 0.27 lower (0.37 to 0.17 lower)        | ⊕⊕⊕⊕ MODERATE | CRITICAL   |
| Frequency of serious adverse events (follow-up 24-30 weeks <sup>1</sup> )                           |                   |                         |                          |                         |                             |                      |                   |                   |                                       |                                            |               |            |
| 4                                                                                                   | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious <sup>2,3</sup> | none                 | 94/769 (12.2%)    | 109/757 (14.4%)   | Risk Difference -0.02 (-0.06 to 0.02) | 2 fewer per 100 (from 6 fewer to 2 more)   | ⊕⊕⊕⊕ LOW      | CRITICAL   |
| Global clinical impression (follow-up 24 weeks; Better indicated by lower values)                   |                   |                         |                          |                         |                             |                      |                   |                   |                                       |                                            |               |            |
| 3                                                                                                   | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious <sup>4</sup>        | none                 | 666               | 649               | -                                     | SMD 0.20 lower (0.31 to 0.09 lower)        | ⊕⊕⊕⊕ MODERATE | CRITICAL   |

<sup>1</sup> Tariot2004, Porsteinsson2008 und Grossberg2008: 24 weeks, Howard2012: 30 weeks

<sup>2</sup> Metaanalysis confidence interval contains positive and negative values

<sup>3</sup> Howard2012: wide confidence interval

<sup>4</sup> Wide confidence intervals in individual studies

# Účinky kognitiv na BPSD se kombinují

- **Memantin – jednotlivé položky NPI:**

- Agitovanost/Agrese ( $p=0.008$ )
- Vznik agrese v průběhu terapie ( $p<0.01$ )
- Bludy ( $p=0.04$ )
- Deprese/dysforie ( $p=0.07$ )

- **Donepezil – jednotlivé položky NPI:**

- Apatie/netečnost ( $p<0.05$ )
- Úzkost ( $p<0.05$ )
- Deprese/dysforie ( $p<0.05$ )

- **Memantin – agitovanost, agrese, bludy**

- **iAChE – apatie, úzkost, netečnost**

# BPSD

## KONSENZUÁLNÍ DOPORUČENÍ PRO KLINICKOU PRAXI

1. Panel doporučuje při vzniku BPSD identifikovat jednotlivé symptomy, primární symptom (např. agitovanost vyvolaná úzkostí, agrese vyvolaná depresí/psychózou) a okolnosti jeho vzniku (co předcházelo, kdo byl přítomen aj.); pátrat po příčinách stavu: tělesná onemocnění (infekce, obstrukce, retence moči aj.), psychické poruchy (úzkost, deprese, psychóza), vliv léků, diskomfort (nadměrná/nedostatečná zevní stimulace, senzorický deficit aj.), nepochopení situace v důsledku kognitivní poruchy, nevhodné jednání pečujících; zaměřit se cíleně na možnost přítomnosti bolesti (např. u nerozpoznané fraktury) – BPSD mohou být jediným příznakem těchto poruch (**silné doporučení**). Panel doporučuje dle zjištěné příčiny zahájit vhodnou intervenci (např. vysadit nevhodný lék, nasadit antibiotika, zajistit klid) a následně hodnotit její efekt (**silné doporučení**).
2. Panel doporučuje u BPSD intervenci vždy zahájit nefarmakologickými přístupy (edukace, terapie reminiscenční, validační, kognitivně/senzoricky stimulační, terapie jasným světlem, tělesné aktivity, aromaterapie, personalizovaná hudba aj.), ty přizpůsobit konkrétní situaci a konkrétním potřebám, preferencím a schopnostem pacienta a pokračovat v nich i v dalším průběhu léčby BPSD; zaměřit se na edukaci pečujících a řešení konkrétních problémů (viz bod 1) (**silné doporučení**).
3. Panel navrhuje v indikovaných případech nasadit kognitiva (IACHe zejména u apatie a psychózy, memantin u agitovanosti a bludů) a/nebo optimalizovat jejich dávku (**slabé doporučení**). Panel doporučuje v případech, kdy BPSD způsobují pacientovi výrazný diskomfort nebo narušují péči o něj a nefarmakologické/psychoterapeutické přístupy (ev. nasazené kognitivum) nemají dostatečný efekt, nasadit jiná psychofarmaka; lék volit dle symptomů (antidepresiva u deprese či úzkosti apod.) (**silné doporučení**).
4. Panel doporučuje nasadit antipsychotika pouze v případech, kdy jsou BPSD, konkrétně psychotické příznaky a/nebo agitovanost/agrese pro nemocného a/nebo osoby v okolí významně stresující/rizikové, nereagují na nefarmakologické přístupy a přetrvávají i při léčbě kognitivu, ev. SSRI (**silné doporučení**). Panel doporučuje individuálně zvažovat poměr benefitu a rizik antipsychotik, začít vždy nízkou dávkou, tu podle potřeby pomalu zvyšovat, monitorovat efekt a případný rozvoj nežádoucích účinků (**silné doporučení**).
5. Panel navrhuje podat psychofarmakum (antipsychotikum a/nebo benzodiazepin) ihned souběžně s nefarmakologickými postupy v případech, kdy chování pacienta vede k ohrožení jeho nebo jeho okolí (např. těžká psychóza, auto- či heteroagrese) a není možná jiná účinná intervence (závažné BPSD jsou indikací k psychiatrické intervenci/hospitalizaci) (**slabé doporučení**).

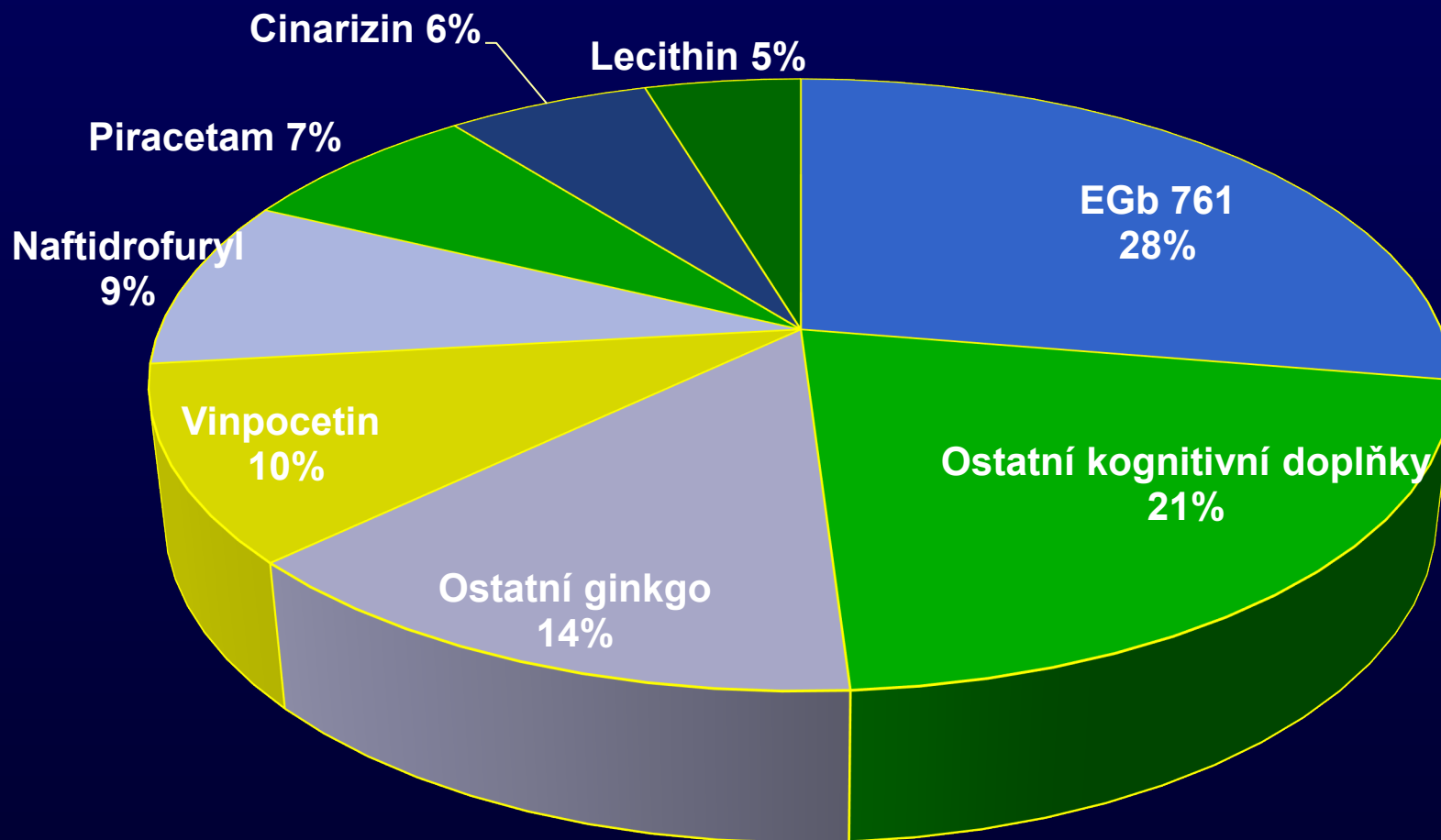
6. Panel navrhuje v léčbě depresivní/úzkostné poruchy u demence používat z antidepresiv jako první volbu SSRI (preferenčně sertralin či escitalopram pro minimální riziko lékových interakcí a příznivý receptorový profil) (**slabé doporučení**), panel navrhuje jako alternativu mirtazapin (**slabé doporučení**). Panel navrhuje u agitovanosti podat SSRI (evidence je pro citalopram) (**slabé doporučení**). Panel navrhuje v případech agrese a psychózy použít antipsychotika 2. generace, nejsilnější průkaz efektu má risperidon (**slabé doporučení**). Panel navrhuje zejména při nutnosti parenterální aplikace jako další volbu haloperidol (**slabé doporučení**)\*. Panel navrhuje v případech výrazné úzkosti zejména s psychomotorickým neklidem a/nebo při potřebě akutní intervence zvážit podání benzodiazepinu, volit lék s kratším vylučovacím poločasem v nízké dávce a po co nejkratší dobu (optimálně jednorázově) (**slabé doporučení**). Panel doporučuje při volbě léku vždy individuálně zvažovat poměr rizika a benefitu (**silné doporučení**).
7. Panel doporučuje při podávání antipsychotik u BPSD pravidelně kontrolovat nutnost jejich podávání a případné nežádoucí účinky (každé 1–2 týdny); po odeznění příznaků po cca 4–12 týdnech (dle závažnosti symptomů) pomalu dávku antipsychotika snižovat až k případnému vysazení (pokud se při snižování dávky symptomy znovu objeví, vrátit se k nejbližší ještě účinné dávce, není-li možná jiná intervence, a v té pak pokračovat do dalšího pokusu o vysazení) (**silné doporučení**). Panel doporučuje nepodávat antipsychotika rutinně déle než tři měsíce, při rozvoji nežádoucích účinků nebo jiných rizik dávku léku snížit nebo lék vysadit (**silné doporučení**).
8. Panel navrhuje v případě psychotických symptomů u demence u Parkinsonovy nemoci a demence s Lewyho tělísky nasadit IACHe (**slabé doporučení**). Panel navrhuje vyhýbat se antipsychotikům (riziko závažných nežádoucích účinků!), nasadit je s velkou opatrností (quetiapin, ev. klozapin) pouze při nutnosti akutní intervence nebo při neúčinnosti IACHe a dalších opatření (revize farmakoterapie, nefarmakologické přístupy aj.) (**slabé doporučení**).
9. Panel navrhuje v prevenci (i léčbě) BPSD individualizovaný přístup k pacientovi se zohledněním jeho osobnostních charakteristik, zájmů, hodnot a dovedností, klást důraz na přiměřeně stimulující prostředí a program, pravidelný denní rozvrh, tělesnou aktivitu, péči o tělesný/psychický stav, zajištění sociálních kontaktů, racionalizaci užívání léků, poradenství, edukaci a podporu pečujících a zajištění potřebné pomoci; preventivní efekt mohou mít kognitiva (**slabé doporučení**).

v ČR máme k dispozici antipsychotika tiaprid a melperon, která používáme často jako 1. a 2. volbu – viz text níže.

# antidepressiva

- Mirtazapin
- Sertralin
- Escitalopram

# Volně prodejné léky (kusů/rok 2023)



**437 mil Kč**

Zdroj IQVIA YTD12/2023

# EGb761

## *Ginkgo biloba* Extract EGb 761 in the Treatment of Patients with Mild Neurocognitive Impairment: A Systematic Review

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**Background:** Many clinical trials testing *Ginkgo biloba* extract EGb 761 in patients with mild forms of cognitive impairment were conducted before widely accepted terms and diagnostic criteria for such conditions were available. This makes it difficult to compare any results from earlier and more recent trials. The objective of this systematic review was to provide a descriptive overview of clinical trials of EGb 761 in patients who met the diagnostic criteria for mild neurocognitive disorder (mild NCD) according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5).

**Methods:** MEDLINE, PubMed and EMBASE were searched for randomized, placebo-controlled double-blind trials of EGb 761 in mild impairment of cognitive functioning. All trials involving patients who met retrospectively applied diagnostic criteria for mild NCD were included. Trials of primary prevention of dementia and trials of combinations of medical treatments were excluded.

**Results:** Among 298 records found in databases and 76 further records related to EGb 761 in references of systematic reviews, 9 reports on clinical trials involving 946 patients met the pre-specified criteria for inclusion. Beneficial effects of EGb 761 were seen in neuropsychological tests (8 of 9 studies), scales for neuropsychiatric symptoms (3 of 3 studies), geriatric rating scales (1 of 2 studies) and global ratings of change (1 of 1 study). Significant effects were found in several domains of cognition (memory, speed of processing, attention and executive functioning). Among the neuropsychiatric symptoms, depression (2 of 3 studies) and anxiety (1 of 1 study) were significantly improved. No differences between EGb 761 treatment and placebo were seen with regard to the rates of adverse events.

**Discussion:** The included studies demonstrate treatment benefits of *Ginkgo biloba* extract EGb 761, mainly on cognitive deficits and neuropsychiatric symptoms, in patients with mild NCD. The drug was safe and well tolerated.

# Retrospektivní kohortová studie

Journal of Alzheimer's Disease 86 (2022) 703–709  
DOI 10.3233/JAD-215348  
IOS Press

703

## Association Between *Ginkgo Biloba* Extract Prescriptions and Dementia Incidence in Outpatients with Mild Cognitive Impairment in Germany: A Retrospective Cohort Study

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Accepted 27 December 2021

Pre-press 3 February 2022

### Abstract.

**Background:** Clinical trials have demonstrated a significant effectiveness of *Ginkgo biloba* extract in patients with mild cognitive impairment (MCI) and dementia.

**Objective:** The present study aims to analyze the impact of *Ginkgo biloba* extract prescriptions on dementia incidence in outpatients with mild cognitive impairment (MCI) in a real-world setting.

**Methods:** This retrospective study was based on the IQVIA Disease Analyzer database and included patients aged 65 or older with a first diagnosis of MCI from January 2000 to December 2019. Each patient was followed for up to 20 years after MCI diagnosis until February 2021. Date of the first diagnosis of dementia or loss to follow-up, whichever occurred first, was noted. To estimate the association between *Ginkgo biloba* prescriptions during the follow-up and dementia incidence, a multivariable Cox regression analysis was performed, adjusted for age, sex, health insurance, documented co-diagnoses, and prescription of cholinesterase inhibitors.

**Results:** Overall, 24 483 MCI patients (mean age: 77.0 years, 56.3% women) were included. It was found that > 2 prescriptions of *Ginkgo biloba* were significantly associated with a reduced dementia incidence (HR: 0.71 (95% CI: 0.55–0.91),  $p = 0.007$ ), as compared with no *Ginkgo biloba* prescription. The effect of receiving > 3 *Ginkgo biloba* prescriptions was even stronger, with an HR of 0.64 (95% CI: 0.48–0.86),  $p = 0.003$ , while for > 4 prescriptions the HR was 0.58 (95% CI: 0.41–0.82) ( $p = 0.002$ ).

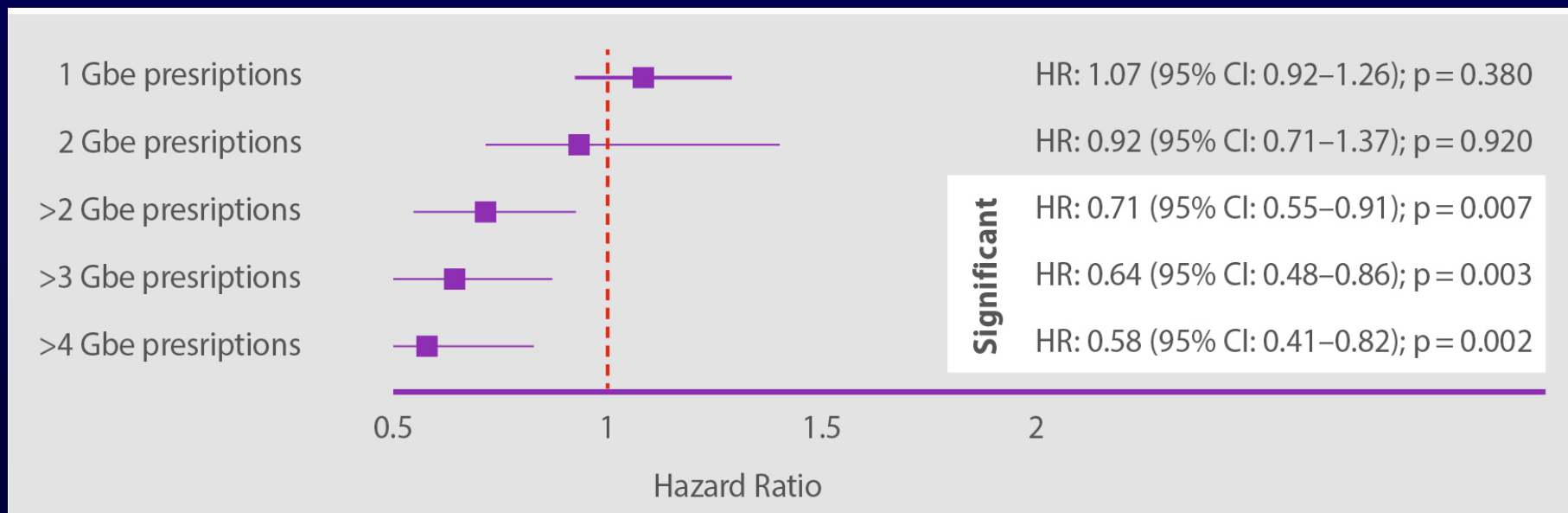
**Conclusion:** All-cause dementia incidence decreased with higher numbers of *Ginkgo biloba* prescriptions in MCI patients.

**Keywords:** Dementia, *Ginkgo biloba* extract, mild cognitive impairment, outpatients



# Více než 2 preskripce EGb761

MCI pacienti s více než 2 Ginkgo preskripcemi: snížení rizika demence



# Ginkgo – jak se v tom orientovat?

- Shoda – rozdíly ginkgo vs. Egb 761
- Shoda - dávky až 240 mg denně (Tebokan 2x 120mg tbl)
- Shoda – vaskulární složka

# Egb761 a ovlivnění srážení krve

- EGb 761 zlepšuje **elasticitu erytrocytů** tím, že chrání jejich buněčnou membránu před oxidačním stresem. Tím **snižuje viskozitu krve a zlepšuje mikrocirkulaci**. Tento účinek nemá vliv na srážení krve.
- Ginkgolid B je antagonist PAF. Terapeutické dávky nejsou u lidí klinicky relevantní pro srážení krve.

## Důkazy:

- Žádné ovlivnění doby krvácení, hemostázy, agregace trombocytů a fibrinolýzy, rizika krvácení (Bal Dit Sollier et al., 2003; Bone, 2008, Kloft & Hörr, 2021)
- Potvrzeno u 1985 a 6415 pacientů v metaanalýzách 18 a 44 klinických studií (Kellermann & Kloft, 2011, Schulz et al., 2017).
- V americké studii více než 1 500 zdravých starších osob užívalo 240 mg EGb 761 + případně ASA po dobu více než 6 let. Míra závažného krvácení byla 8,9 %, zatímco ve skupině s placebem 9,2 % (Dekosky et al., 2008)
- Analýza 320 644 anamnéz pacientů z německé databáze MediPlus: žádná kumulace krvácení u uživatelů EGb 761 (n = 9 794, relativní riziko 0,99) ve srovnání s jakýmkoli lékem proti demenci (relativní riziko 1,05); (Gaus et al., 2005).

# Egb761 a interakce

## **SPC Tebikan: Žádné klinicky relevantní interakce**

### **Žádný klinicky významný interakční potenciál EGb 761**

- při maximálních terapeutických dávkách (Markowitz 2003, Gurley 2002, Gurley 2005, Zadoyan 2012, Unger 2013)

### **EGb 761 a kyselina acetylsalicylová (ASA)**

- žádné klinicky relevantní interakce (Wolf, 2006; Gardner et al., 2007, Kloft & Hörr, 2021)

### **EGb 761 a warfarin**

- žádné klinicky relevantní interakce (Jiang et al., 2005, Kloft & Hörr, 2021)
  - SPC: "**Dostupné studie s warfarinem nenaznačují, že existuje interakce mezi warfarinem a přípravky G. biloba**, ale doporučuje se adekvátní sledování při zahájení, při změně dávky G. biloba, při ukončení příjmu G. biloba nebo při změně produktu."

### **EGb 761 a rivaroxaban (Xarelto®)**

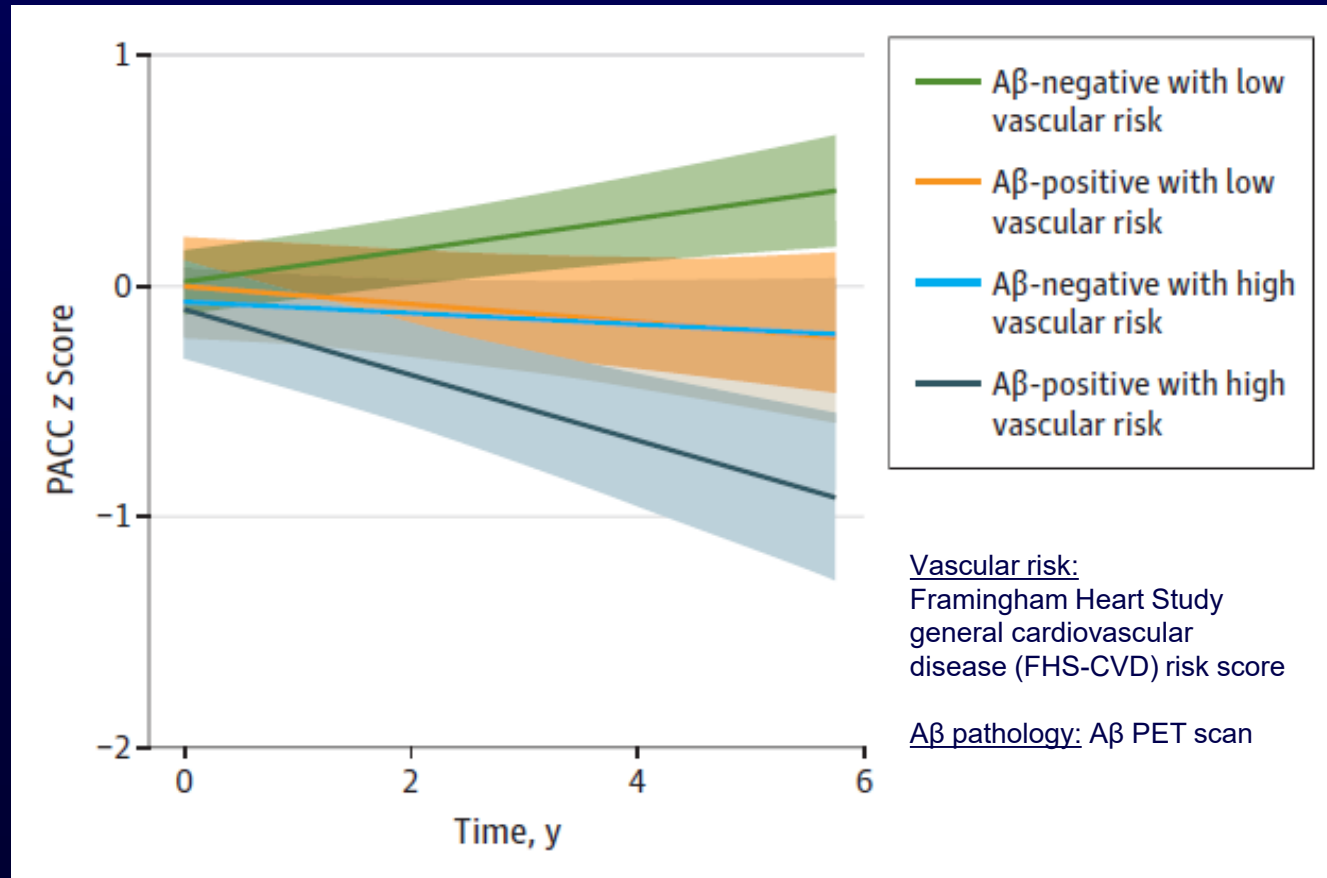
- žádné nežádoucí příhody indikující krvácení, žádné klinicky významné změny hematologických parametrů
- žádný vliv na plazmatické koncentrace rivaroxabanu ani na antifaktorovou aktivitu Xa (Hörr et al., 2022)

# Z hlášení nežádoucích účinků

- **Za 60 let** bylo **celosvětově** publikováno **12 kazuistik krvácení** u pacientů, kteří užívali přípravky z *Ginkgo biloby* ( Ernst et al., 2005).
- V **1** z případů **EGb 761**, v dalším jiný přípravek; v ostatních 10 přípravky neznámého složení.
- U jednoho pacienta, který užíval **EGb 761** (3 - 4 x 40 mg denně po dobu 6 měsíců) **nebylo prokázáno**, že by krvácení souviselo s užíváním *Ginkgo biloby*.
- **V tomto roce** (2002), bylo jen v **Německu** užito přibližně **175 milionů denních dávek (240 mg)** monopreparátů z **ginkga\***.
- \*V roce 2002 bylo v lékárnách v Německu zakoupeno 6,6 milionu balení monopreparátů Ginkgo. 1,9 milionu balení přípravku Tebonin (přibližně 50,7 milionu 240 mg denních dávek) odpovídalo tržnímu podílu přibližně 29 %. To znamená, že užívání monopřípravků Ginkgo v celém Německu lze odhadnout na přibližně 175 milionů 240 mg denních dávek. (Zdroj: IQVIA, dříve IMS Frankfurt, Pharmascope national, kalendářní rok 2002; vlastní výpočty).

# Alzheimer + vaskulární

**Harvard Aging Brain Study**, 223 clinically normal older adults  
(58.3% female, mean age 73.7 (sd 6.0) years, mean follow-up 3.7 years)



# Alzheimerova nemoc – nové léky



# Komorbidity – revize ATN kriterií 2024

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| Received: 7 February 2024   Revised: 21 March 2024   Accepted: 4 April 2024                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |  |
| DOI: 10.1002/alz.13859                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |
| Alzheimer's & Dementia<br>THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |  |
| RESEARCH ARTICLE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |
| Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |  |
| Clifford R. Jack Jr. <sup>1</sup>   J. Scott Andrews <sup>2</sup>   Thomas G. Beach <sup>3</sup>   Teresa Buracchio <sup>4</sup>   Billy Dunn <sup>5</sup>   Ana Graf <sup>6</sup>   Oskar Hansson <sup>7,8</sup>   Carole Ho <sup>9</sup>   William Jagust <sup>10</sup>   Eric McDade <sup>11</sup>   Jose Luis Molinuevo <sup>12</sup>   Ozioma C. Okonkwo <sup>13</sup>   Luca Pani <sup>14</sup>   Michael S. Rafii <sup>15</sup>   Philip Scheltens <sup>16</sup>   Eric Siemers <sup>17</sup>   Heather M. Snyder <sup>18</sup>   Reisa Sperling <sup>19</sup>   Charlotte E. Teunissen <sup>20</sup>   Maria C. Carrillo <sup>18</sup> |  |

JACK ET AL.

# Alzheimer's & Dementia\*

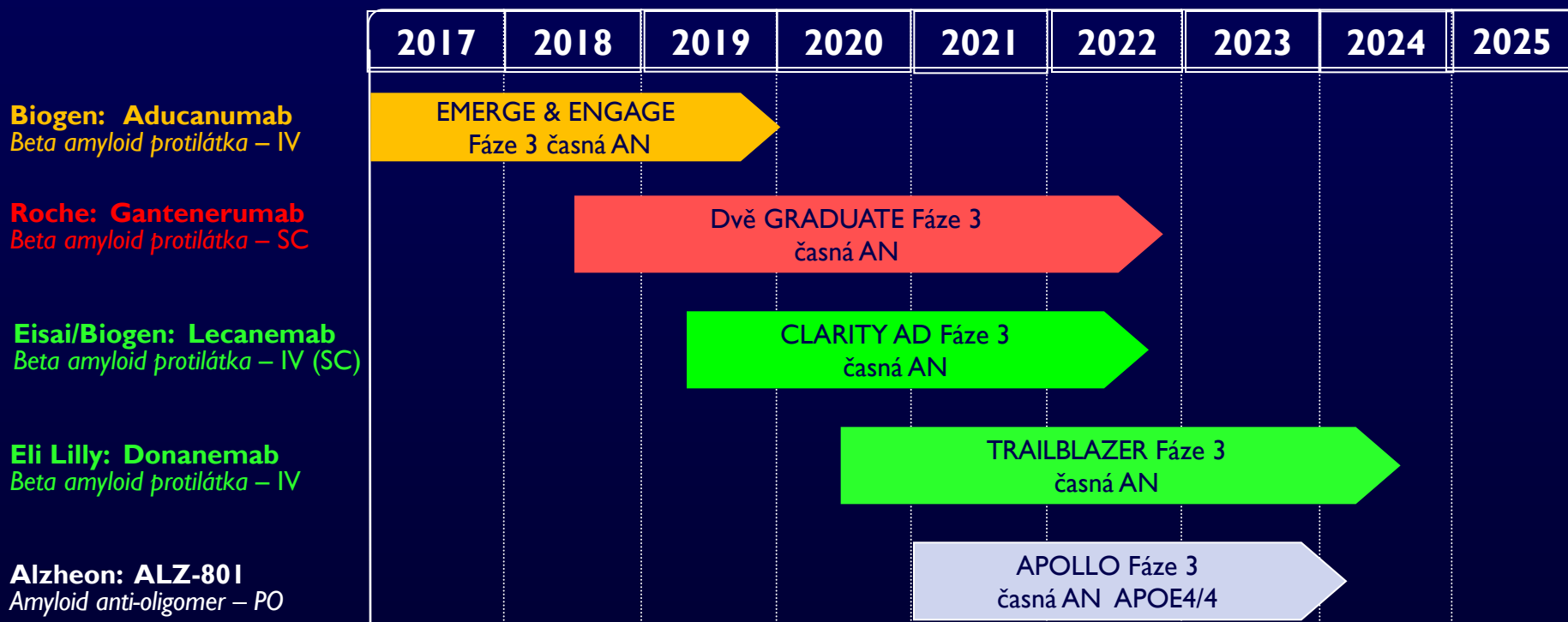
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

**TABLE 2** Intended uses for imaging, CSF, and plasma biomarker assays.

| Intended use                                                              | CSF                                                                                          | Plasma                                          | Imaging                      |
|---------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|-------------------------------------------------|------------------------------|
| <b>Diagnosis</b>                                                          |                                                                                              |                                                 |                              |
| A: (A $\beta$ proteinopathy)                                              | —                                                                                            | —                                               | Amyloid PET                  |
| T <sub>1</sub> : (phosphorylated and secreted AD tau)                     | —                                                                                            | p-tau217                                        | —                            |
| Hybrid ratios                                                             | p-tau181/A $\beta$ 42, t-tau/A $\beta$ 42, A $\beta$ 42/40                                   | %p-tau217                                       | —                            |
| <b>Staging, prognosis, as an indicator of biological treatment effect</b> |                                                                                              |                                                 |                              |
| A: (A $\beta$ proteinopathy)                                              | —                                                                                            | —                                               | Amyloid PET                  |
| T <sub>1</sub> : (phosphorylated and secreted AD tau)                     | —                                                                                            | p-tau217                                        | —                            |
| Hybrid ratios                                                             | p-tau181/A $\beta$ 42, t-tau/A $\beta$ 42, A $\beta$ 42/40                                   | %p-tau217                                       | —                            |
| T <sub>2</sub> : (AD tau proteinopathy)                                   | MTBR-tau243, other p-tau forms (e.g., p-tau205), non-phosphorylated mid-region tau fragments | MTBR-tau243, other p-tau forms (e.g., p-tau205) | Tau PET                      |
| N (injury, dysfunction, or degeneration of neuropil)                      | NfL                                                                                          | NfL                                             | Anatomic MRI, FDG PET        |
| I (inflammation) Astrocytic activation                                    | GFAP                                                                                         | GFAP                                            | —                            |
| <b>Identification of copathology</b>                                      |                                                                                              |                                                 |                              |
| N (injury, dysfunction, or degeneration of neuropil)                      | NfL                                                                                          | NfL                                             | Anatomic MRI, FDG PET        |
| V vascular brain injury                                                   | —                                                                                            | —                                               | Infarction on MRI or CT, WMH |
| S $\alpha$ -synuclein                                                     | $\alpha$ Syn-SAA                                                                             | —                                               | —                            |

|                                                                     |                                                                                                                        |                              |
|---------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|------------------------------|
| TABLE 1 Categorization of fluid analyte and imaging biomarkers.     |                                                                                                                        |                              |
| Biomarker category                                                  | CSF or plasma analytes                                                                                                 | Imaging                      |
| Core Biomarkers                                                     |                                                                                                                        |                              |
| Core 1                                                              |                                                                                                                        |                              |
| A (A $\beta$ proteinopathy)                                         | A $\beta$ 42                                                                                                           | Amyloid PET                  |
| T <sub>1</sub> : (phosphorylated and secreted AD tau)               | p-tau217, p-tau181, p-tau231                                                                                           | —                            |
| Core 2                                                              |                                                                                                                        |                              |
| T <sub>2</sub> (AD tau proteinopathy)                               | MTBR-tau243, other phosphorylated tau forms (e.g., p-tau205), non-phosphorylated mid-region tau fragments <sup>a</sup> | Tau PET                      |
| Biomarkers of non-specific processes involved in AD pathophysiology |                                                                                                                        |                              |
| N (injury, dysfunction, or degeneration of neuropil)                | NfL                                                                                                                    | Anatomic MRI, FDG PET        |
| I (inflammation) Astrocytic activation                              | GFAP                                                                                                                   | —                            |
| Biomarkers of non-AD comorbidity                                    |                                                                                                                        |                              |
| V vascular brain injury                                             | —                                                                                                                      | Infarction on MRI or CT, WMH |
| S $\alpha$ -synuclein                                               | $\alpha$ Syn-SAA <sup>a</sup>                                                                                          | —                            |

# Biologická léčba - ovlivnění A $\beta$



[in](#)[X](#)[f](#)[+](#)

BIOTECH

# Alzheon Alzheimer's drug knocked down in pivotal APOLLOE4 bout

By **Nick Paul Taylor** · Apr 10, 2025 8:48am

[Alzheimer's disease](#)[Alzheimer's drugs](#)[failed trials](#)[Alzheon](#)

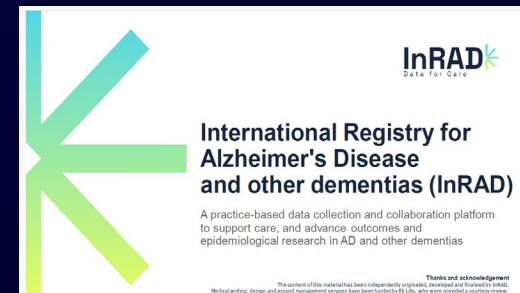
# Aktuální situace

- lecanemab - USA, Japonsko, Čína, Korea, Izrael, UK
  - finálně schváleno EK 15.4.25
  - 9-12 měsíců jednání o úhradě (25/26)
  - heterozygoti ApoE4 a nenosiči
  - infuze 1x/14 dní



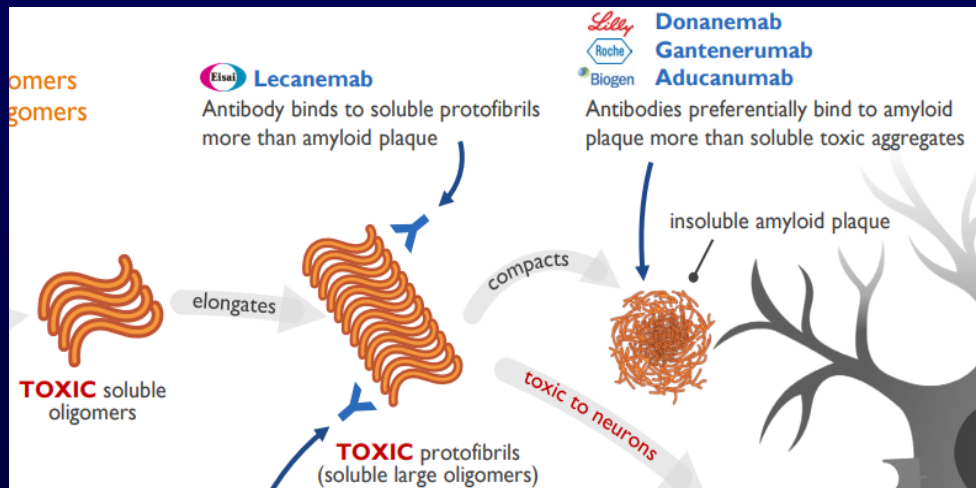
- donanemab - schválen USA, Izrael, Korea, odvolání k EMA
  - infuze 1x měsíčně
  - pouze nenosiči?

- Controlled access program – razítko, registr

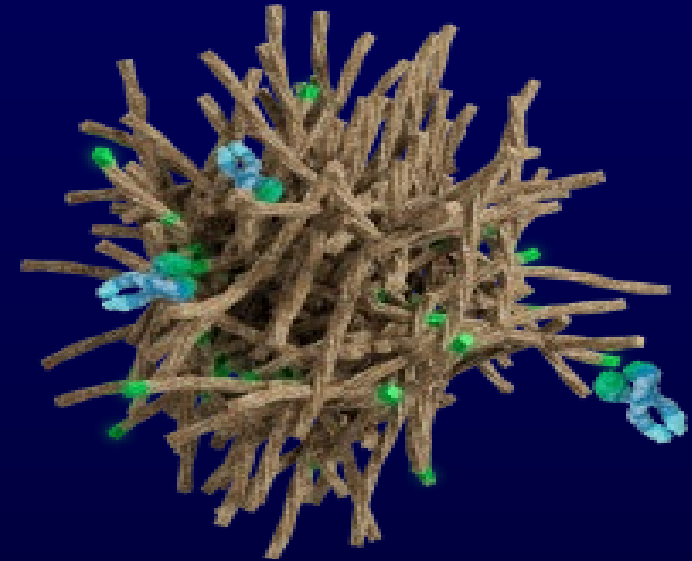


# Monoklonální protilátky - nová třída léků proti A $\beta$

- Rozdíly: - vazebné místo:



Lecanemab cílí na A $\beta$  oligomery



Donanemab cílí na A $\beta$  plaky N3pG



- design studií
- různé populace pacientů = personalizace

# 7/2023 – schválení FDA

*The NEW ENGLAND JOURNAL of MEDICINE*

## ORIGINAL ARTICLE

### Lecanemab in Early Alzheimer's Disease

C.H. van Dyck, C.J. Swanson, P. Aisen, R.J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

## ABSTRACT

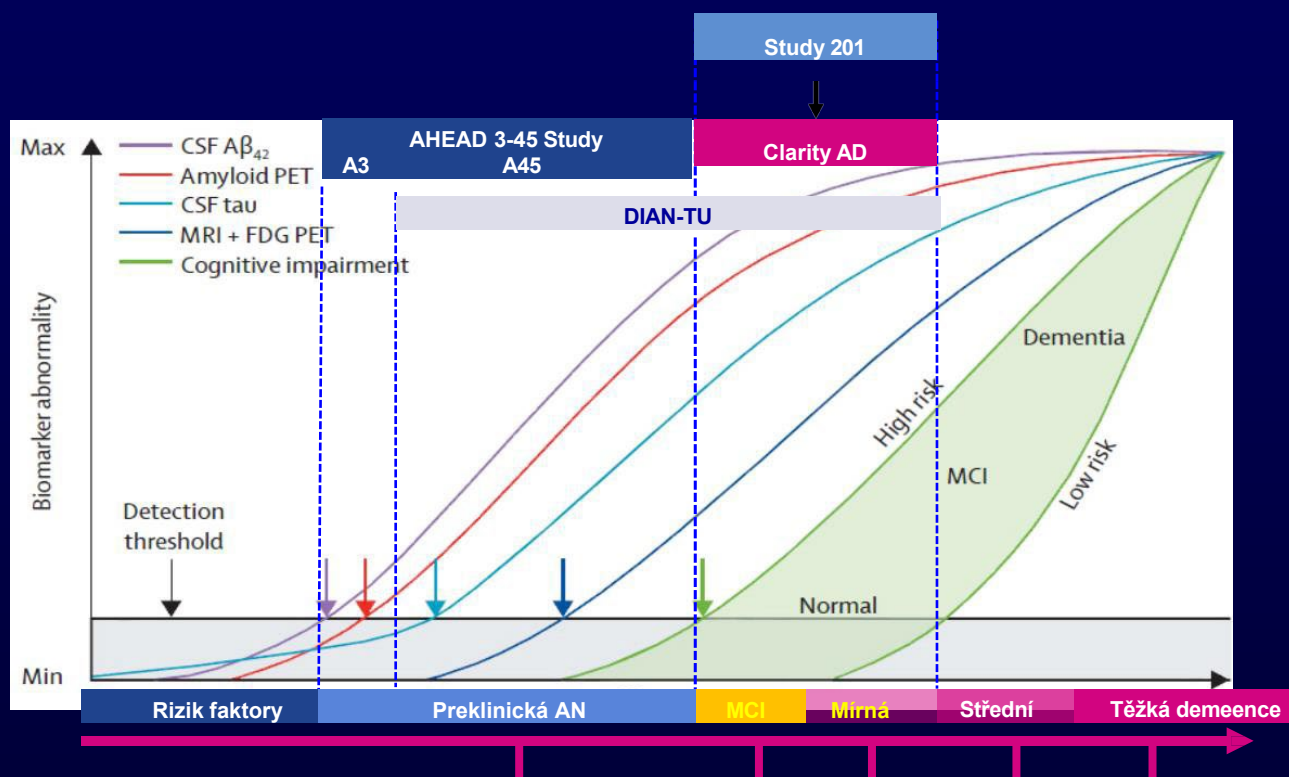
#### BACKGROUND

The accumulation of soluble and insoluble aggregated amyloid-beta ( $A\beta$ ) may initiate or potentiate pathologic processes in Alzheimer's disease. Lecanemab, a humanized IgG1 monoclonal antibody that binds with high affinity to  $A\beta$  soluble protofibrils, is being tested in persons with early Alzheimer's disease.

#### METHODS

We conducted an 18-month, multicenter, double-blind, phase 3 trial involving persons 50 to 90 years of age with early Alzheimer's disease (mild cognitive impairment or mild dementia due to Alzheimer's disease) with evidence of amyloid on positron-emission tomography (PET) or by cerebrospinal fluid testing. Participants were randomly assigned in a 1:1 ratio to receive intravenous lecanemab (10 mg per kilogram of body weight every 2 weeks) or placebo. The primary end point was the change from baseline at 18 months in the score on the Clinical Dementia Rating–Sum of Boxes (CDR-SB; range, 0 to 18, with higher scores indicating greater impairment). Key secondary end points were the change in amyloid burden on PET, the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14; range, 0 to 90; higher scores indicate greater impairment), the

# Kontinuum AN a lecanemab studie



Normální  
kognice

soběstační

nesoběstační

# Clarity – 1795 pacientů, 18 měsíců

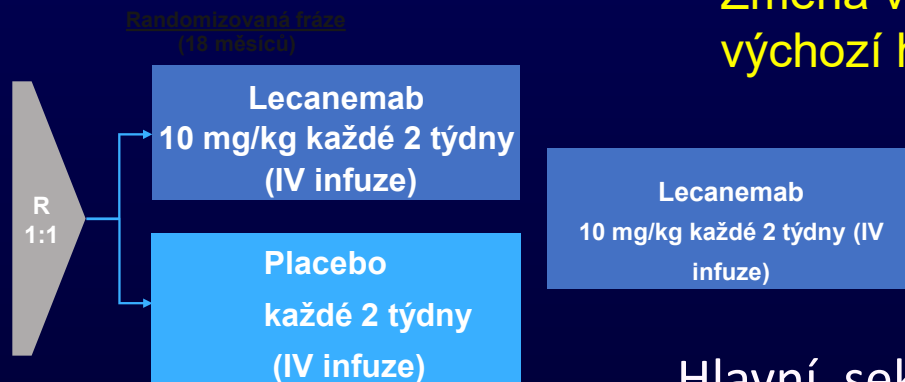
- Globální placebem kontrolovaná, dvojitě zaslepená, randomizovaná studie s paralelními skupinami

## Populace pacientů

MCI při AN

Lehká AN demence

- Potvrzený amyloid
- MMSE 22 - 30
- WMS-IV LMSII  $\geq 1$  SD



Primární cíl:

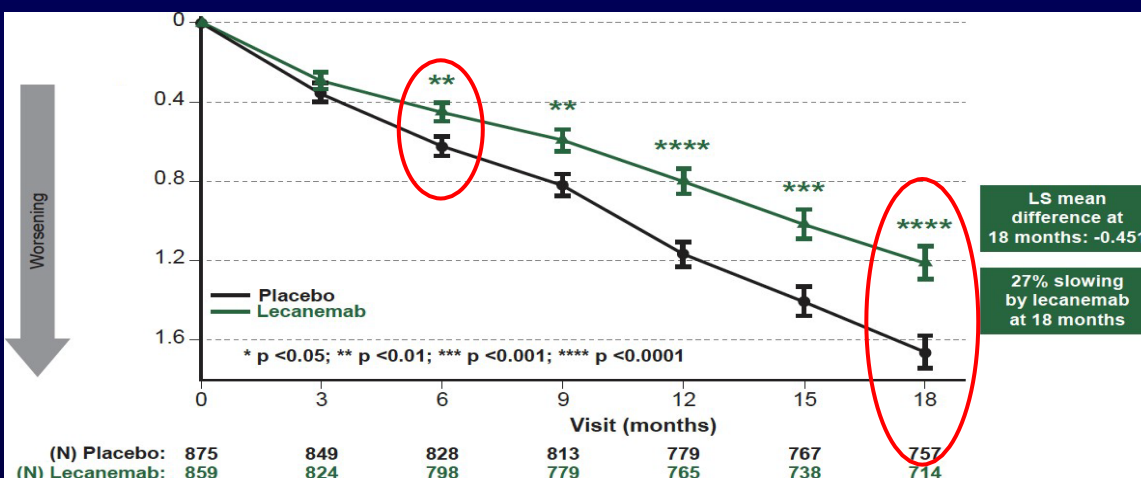
- Změna v CDR-SB oproti výchozí hodnotě za 18 měsíců

Hlavní sekundární cíle:

- Změna oproti výchozímu stavu po 18 měsících:
  - amyloid PET
  - ADAS-Cog14
  - ADCS MCI-ADL

# Lecanemab - soběstačnost (CDR-SB)

- Lecanemab u všech AN pacientů (včetně homozygotů) zpomalil progresi o 27%**



## HIGHLIGHTS OF PRESCRIBING INFORMATION

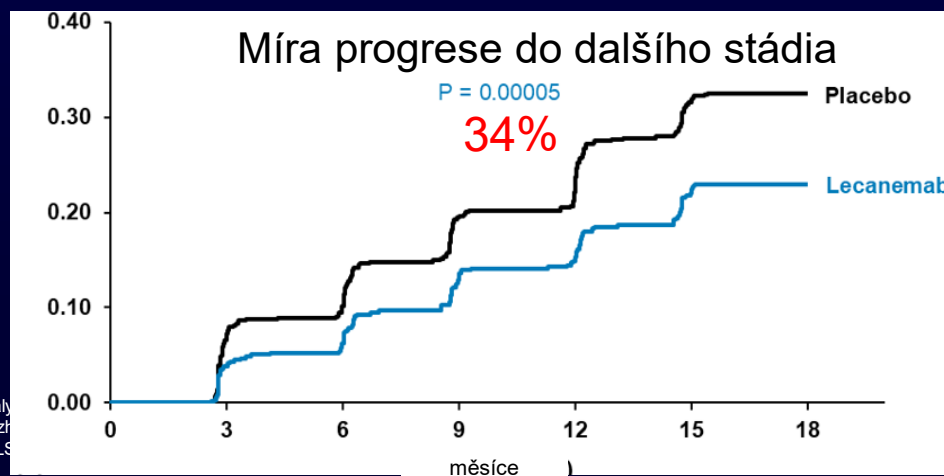
These highlights do not include all the information needed to use LEQEMBI™ safely and effectively. See full prescribing information for LEQEMBI™.

LEQEMBI™ (lecanemab-irmb) injection, for intravenous use  
Initial U.S. Approval: 2023

## INDICATIONS AND USAGE

LEQEMBI is an amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease. Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with LEQEMBI. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial. (1)

- Lecanemab u heterozygotů ApoE4 a nenosičů zpomalil progresi o 34 %**

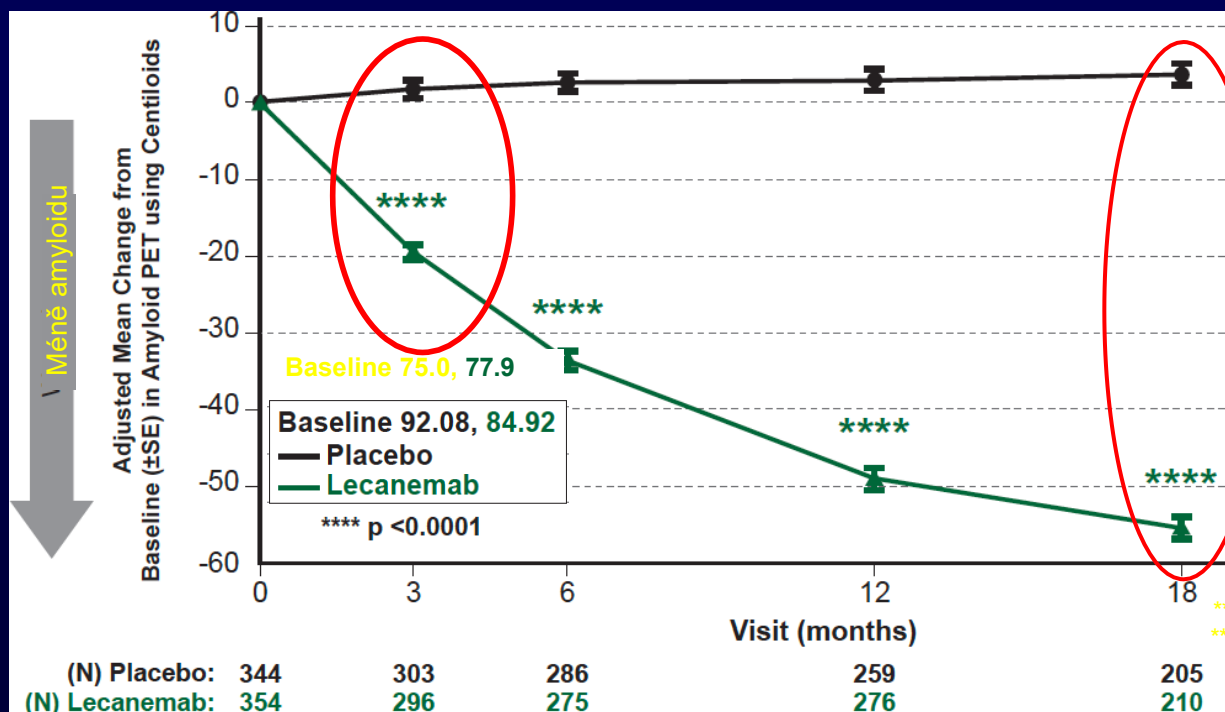


Note: Based on modified intention-to-treat analysis by visit interaction, clinical subgroup, use of Alzheimer's Disease Rating Scale (ADRS), Clinical Dementia Rating, sum of boxes; LS

MMRM) with treatment group, visit, treatment group fixed effects, and baseline value as covariate.

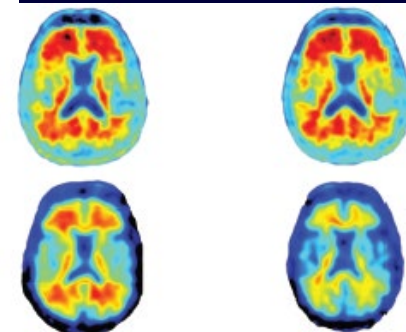
# Studie Clarity – amyloid PET

**Lecanemab snížil amyloidní zátěž ve všech časových bodech počínaje 3. měsícem**



Mean <30  
Centiloids for  
lecanemab at 18  
months\*

Difference of  
-59.1 Centiloids  
at 18 months



\*After 18 months of treatment, the average amyloid level was 23 Centiloids in the lecanemab treatment group in the amyloid PET substudy, which is below the threshold for amyloid positivity of participants are considered to have elevated brain amyloid.

\*\* 73 subjects were not included at 18 months (per Statistical analysis plan) since their PET assessments were performed after receiving lecanemab in the extension phase.

Note: Based on pharmacodynamic analysis population (amyloid PET substudy population). Adjusted mean change from baseline, standard error (SE) and p-value are derived using mixed model visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE4 carrier status, region, baseline value by visit interaction as fixed effects. PET: positron emission tomography. SE, standard error.

# donanemab (KISUNLA)

JAMA | Original Investigation

## Donanemab in Early Symptomatic Alzheimer Disease The TRAILBLAZER-ALZ 2 Randomized Clinical Trial

John R. Sims, MD; Jennifer A. Zimmer, MD; Cynthia D. Evans, PhD; Ming Lu, MD, MS, MPH; Paul Ardayfio, PhD; JonDavid Sparks, PhD; Alette M. Wessels, PhD; Sergey Shcherbinin, PhD; Hong Wang, PhD; Emel Serap Monkul Nery, MD; Emily C. Collins, PhD; Paul Solomon, PhD; Stephen Salloway, MD; Liana G. Apostolova, MD; Oskar Hansson, MD, PhD; Craig Ritchie, MD, PhD; Dawn A. Brooks, PhD; Mark Mintun, MD; Daniel M. Skovronsky, MD, PhD; for the TRAILBLAZER-ALZ 2 Investigators

**IMPORTANCE** There are limited efficacious treatments for Alzheimer disease.

**OBJECTIVE** To assess efficacy and adverse events of donanemab, an antibody designed to clear brain amyloid plaque.

**DESIGN, SETTING, AND PARTICIPANTS** Multicenter (277 medical research centers/hospitals in 8 countries), randomized, double-blind, placebo-controlled, 18-month phase 3 trial that enrolled 1736 participants with early symptomatic Alzheimer disease (mild cognitive impairment/mild dementia) with amyloid and low/medium or high tau pathology based on positron emission tomography imaging from June 2020 to November 2021 (last patient visit for primary outcome in April 2023).

**INTERVENTIONS** Participants were randomized in a 1:1 ratio to receive donanemab (n = 860) or placebo (n = 876) intravenously every 4 weeks for 72 weeks. Participants in the donanemab group were switched to receive placebo in a blinded manner if dose completion criteria were met.

**MAIN OUTCOMES AND MEASURES** The primary outcome was change in integrated Alzheimer Disease Rating Scale (iADRS) score from baseline to 76 weeks (range, 0-144; lower scores indicate greater impairment). There were 24 gated outcomes (primary, secondary, and exploratory), including the secondary outcome of change in the sum of boxes of the Clinical Dementia Rating Scale (CDR-SB) score (range, 0-18; higher scores indicate greater impairment). Statistical testing allocated  $\alpha$  of .04 to testing low/medium tau population outcomes, with the remainder (.01) for combined population outcomes.

**RESULTS** Among 1736 randomized participants (mean age, 73.0 years; 996 [57.4%] women; 1182 [68.1%] with low/medium tau pathology and 552 [31.8%] with high tau pathology), 1320 (76%) completed the trial. Of the 24 gated outcomes, 23 were statistically significant. The least-squares mean (LSM) change in iADRS score at 76 weeks was -6.02 (95% CI, -7.01 to -5.03) in the donanemab group and -9.27 (95% CI, -10.23 to -8.31) in the placebo group (difference, 3.25 [95% CI, 1.88-4.62];  $P < .001$ ) in the low/medium tau population and -10.2 (95% CI, -11.22 to -9.16) with donanemab and -13.1 (95% CI, -14.10 to -12.13) with placebo (difference, 2.92 [95% CI, 1.51-4.33];  $P < .001$ ) in the combined population. LSM change in CDR-SB score at 76 weeks was 1.20 (95% CI, 1.00-1.41) with donanemab and 1.88 (95% CI, 1.68-2.08) with placebo (difference, -0.67 [95% CI, -0.95 to -0.40];  $P < .001$ ) in the low/medium tau population and 1.72 (95% CI, 1.53-1.91) with donanemab and 2.42 (95% CI, 2.24-2.60) with placebo (difference, -0.7 [95% CI, -0.95 to -0.45];  $P < .001$ ) in the combined population. Amyloid-related imaging abnormalities of edema or effusion occurred in 205 participants (24.0%; 52 symptomatic) in the donanemab group and 18 (2.1%; 0 symptomatic during study) in the placebo group and infusion-related reactions occurred in 74 participants (8.7%) with donanemab and 4 (0.5%) with placebo. Three deaths in the donanemab group and 1 in the placebo group were considered treatment related.

**CONCLUSIONS AND RELEVANCE** Among participants with early symptomatic Alzheimer disease and amyloid and tau pathology, donanemab significantly slowed clinical progression at 76 weeks in those with low/medium tau and in the combined low/medium and high tau pathology population.

 Visual Abstract

 Editorial pages 503, 505, 507, and 510

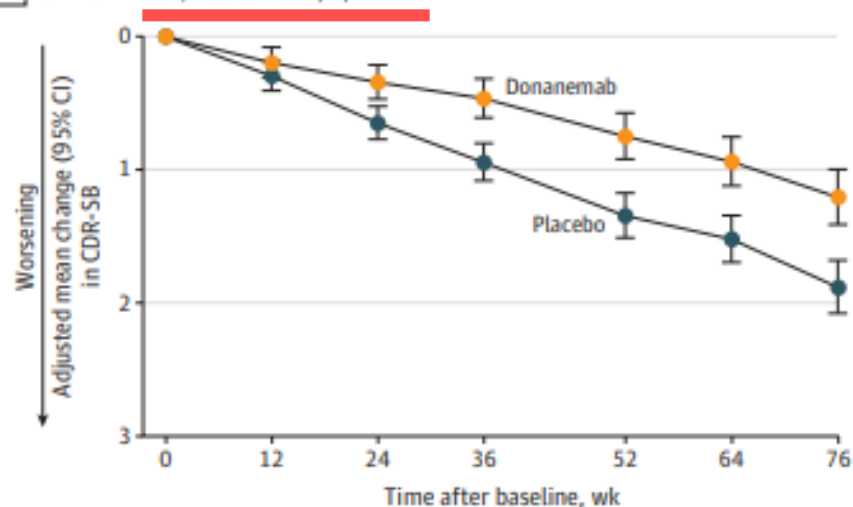
 Supplemental content

**Author Affiliations:** Author affiliations are listed at the end of this article.

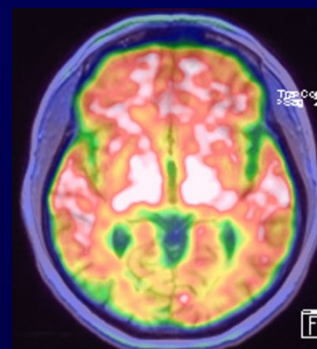
**Group Information:** The TRAILBLAZER-ALZ 2 investigators appear in Supplement 4.

# donanemab (KISUNLA)

**C** CDR-SB in low/medium tau population



|                     |     |     |     |     |     |     |
|---------------------|-----|-----|-----|-----|-----|-----|
| No. of participants |     |     |     |     |     |     |
| Placebo             | 569 | 561 | 540 | 516 | 486 | 461 |
| Donanemab           | 546 | 530 | 499 | 471 | 451 | 418 |



A, 35.1% slowing (95% CI, 19.90%-50.23%) of clinical progression. B, 22.3% slowing (95% CI, 11.38%-33.15%) of clinical progression. C, 36.0% slowing (95% CI, 20.76%-51.15%) of clinical progression. D, 28.9% slowing (95% CI, 18.41%-39.44%) of clinical progression. iADRS data were analyzed using the natural cubic spline model with 2 degrees of freedom (NCS2) and CDR-SB data



# Co změna 0.5-1 v CDR znamená?

**CDR 0.5**  
(velmi mírné postižení)

**CDR 1**  
(mírné postižení)

## Paměť

**Lehká zapomětlivost;**  
neúplné vybavování událostí;  
"benigní" zapomětlivost



**Pokročilá porucha  
paměti;**

zejména recentní události,  
narušeno fungování v  
každodenním životě

## Community affairs

**Mírné postižení**



**Neschopnost fungovat  
samostatně!**

I když se o některé činnosti  
nadále snaží, na první pohled  
nemusí být zřejmě postižení

## Domácnost/ koníčky

Žije doma, má koníčky a zajímá  
se o okolní dění

**mírné postižení**



Zřetelné postižení fungování v  
domácím prostředí;

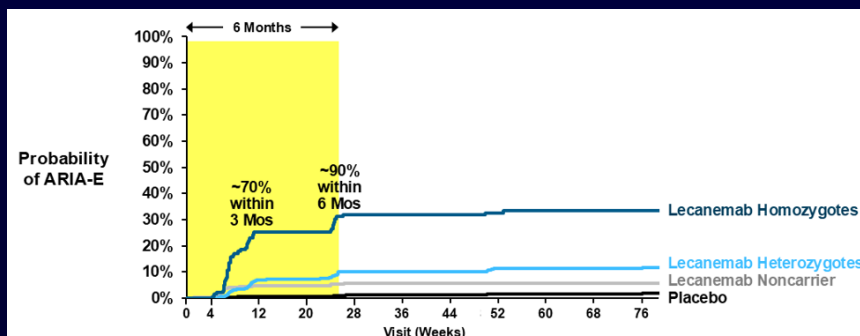
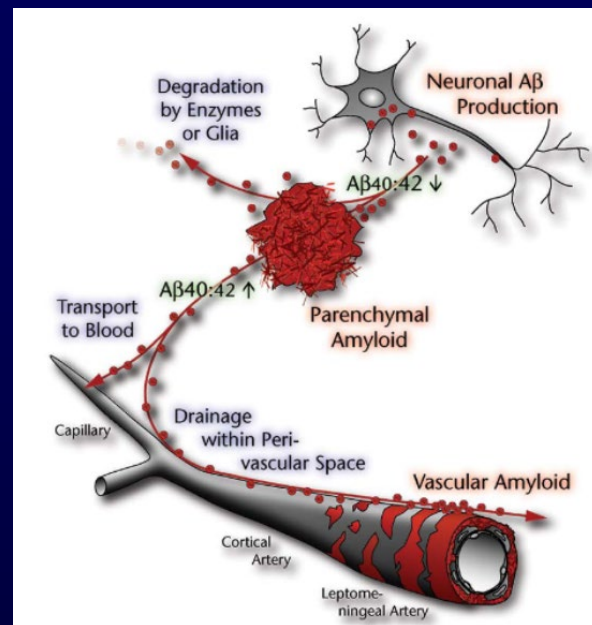
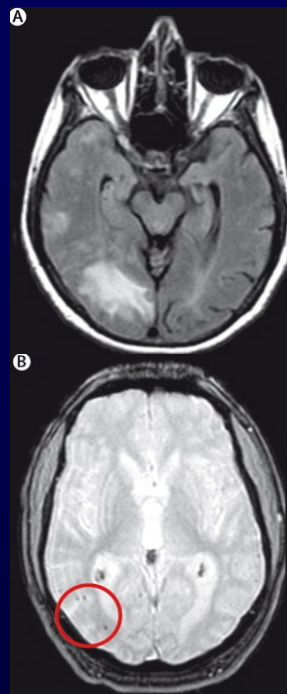
**neschopnost  
složitějších činností;**

Opouští koníčky a zájmy

**Zhoršení kognice a soběstačnosti (o 0.5–1 bod) v časných stádiích AN považuje za významné většina pacientů, rodin a pečujících**

# Vedlejší nežádoucí účinky léčby

- ARIA – E (leca 12.6%)  
(dona 24%)
- ARIA – H (leca 17,3 %)  
(dona 31,4%)



# Amyloid-lowering treatment in Alzheimer's disease

We fully endorse the Editorial<sup>1</sup> on the negative opinion of the European Medicines Agency of the use of lecanemab for the treatment of early

A few thousand patients in the USA and elsewhere in the world are currently receiving lecanemab in clinical practice, following appropriate use recommendations.<sup>3</sup> So far, the side-effect profile appears consistent with what was observed in clinical trials, indicating that lecanemab can be safely administered when inclusion and

\*Frank Jessen, Lutz Frölich, Jakob Hort, Bengt Winblad, Juan Fortea  
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Published online August 11, 2024, <http://dx.doi.org/10.14283/jpad.2024.153>

## Review

## Progress in the Treatment of Alzheimer's Disease Is Needed – Position Statement of European Alzheimer's Disease Consortium (EADC) Investigators

F. Jessen<sup>1,2</sup>, M.G. Kramberger<sup>3,4,5</sup>, D. Angioni<sup>6</sup>, D. Aarsland<sup>7,8</sup>, M. Balasa<sup>9</sup>, K. Bennys<sup>10</sup>, M. Boada<sup>11,12</sup>, M. Boban<sup>13</sup>, A. Chincarini<sup>14</sup>, L. Exalto<sup>15</sup>, A. Felbecker<sup>16</sup>, K. Fliessbach<sup>2,17</sup>, G.B. Frisoni<sup>18</sup>, A.J. Garza-Martínez<sup>19</sup>, T. Grimmer<sup>20</sup>, B. Hanseew<sup>21,22</sup>, J. Hort<sup>23</sup>, A. Ivanoiu<sup>21,22</sup>, S. Klöppel<sup>24</sup>, L. Krajcovicova<sup>25</sup>, B. McGuinness<sup>26</sup>, P. Mecocci<sup>5,27</sup>, A. de Mendonca<sup>28</sup>, A. Nouis<sup>29,30</sup>, P.-J. Ousset<sup>6</sup>, C. Paquet<sup>31</sup>, R. Perneczky<sup>32,33,34,35</sup>, O. Peters<sup>36,37</sup>, M. Tabuas-Pereira<sup>38</sup>, F. Piazza<sup>39</sup>, D. Plantone<sup>40</sup>, M. Riverol<sup>41,42</sup>, A. Ruiz<sup>11,12</sup>, G. Sacco<sup>43,44,45</sup>, I. Santana<sup>46,47,48</sup>, N. Scarmeas<sup>49,50</sup>, E. Solje<sup>51,52</sup>, E. Stefanova<sup>53</sup>, S. Sutovsky<sup>54</sup>, W. van der Flier<sup>55,56</sup>, T. Welsh<sup>57,58,59</sup>, A. Wimo<sup>60</sup>, B. Winblad<sup>60,61</sup>, L. Frölich<sup>62</sup>, S. Engelborghs<sup>63,64,65</sup>

31% reduced risk for advancing to a more severe stage within 18 months (hazard ratio 0.69) can undoubtedly be considered meaningful given that a recent publication has also concluded that the effect size of lecanemab is comparable to those of approved and used biologicals in other diseases.<sup>3</sup>

neurology. *Alzheimer's Dement* 2024; 10: e12500.  
4. Honig LS, Sabbagh MN, van Dyck CH, et al. Updated safety results from phase 3 lecanemab study in early Alzheimer's disease. *Alzheimer's Res Ther* 2024; 16: 105.  
5. Cummings J, Apostolova L, Rabinozici GD, et al. Lecanemab: appropriate use recommendations. *J Prev Alzheimer Dis* 2023; 10: 362-77.

# Stojí to za to?..... Jinde ano...

Received: 16 April 2024 | Revised: 24 July 2024 | Accepted: 25 July 2024  
DOI: 10.1002/trc2.12500

RESEARCH ARTICLE

**Perspectives on the clinical use of anti-amyloid therapy for the treatment of Alzheimer's disease: Insights from the fields of cancer, rheumatology, and neurology**

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<sup>2</sup>The Markey Cancer Center, and the Sanders-Brown Center on Aging, University of Kentucky, Lexington, Kentucky, USA  
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Email: [gregory.jicha@uky.edu](mailto:gregory.jicha@uky.edu)

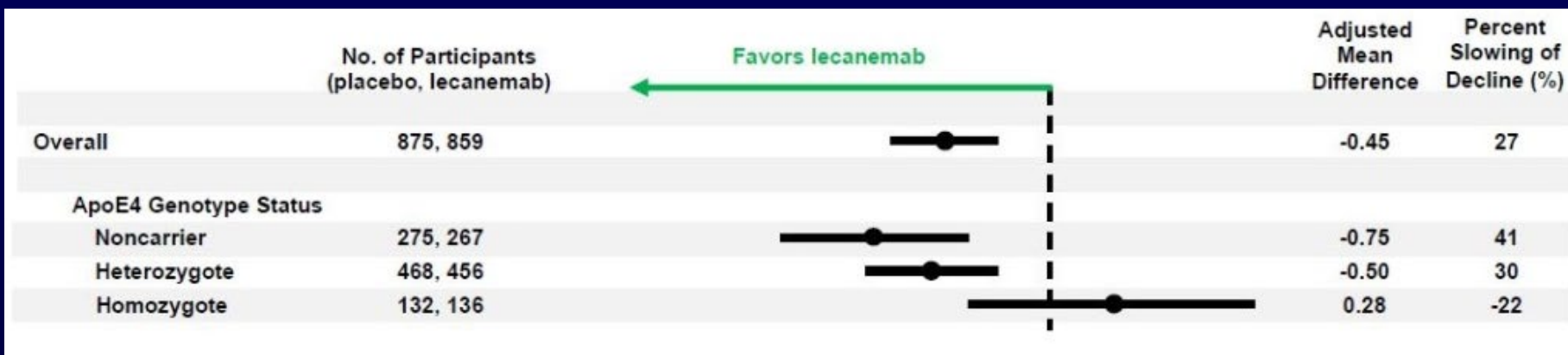
**Funding information**  
National Institutes of Health, Grant/Award Number: P30 AG072946

**Abstract**  
**Introduction:** The advent of disease-modifying therapies for Alzheimer's disease (AD) has raised many questions and debates in the field as to the clinical benefits, risks, and costs of such therapies. The controversies have resulted in the perception that many clinicians are apprehensive about prescribing these medications to their patient populations. There also remains widespread uncertainty as to the economic impact, cost benefit ratio, and safety oversight for use of these medications in standard clinical care settings.  
**Methods:** To contextualize such issues, the present study compared anti-amyloid biologic therapy (lecanemab) to four commonly used biologic agents in other fields, including trastuzumab for breast cancer, bevacizumab for lung cancer, etanercept for rheumatoid arthritis, and ocrelizumab for multiple sclerosis.  
**Results:** The data presented demonstrate comparable costs, clinical benefits, and risks for these biologic agents in their disparate disease states.  
**Discussion:** These results provide context for the costs, clinical benefits, and safety regarding the mainstream use of anti-amyloid biologic agents for the prevention of cognitive loss. While the era of disease-modifying therapies for AD is now in its infancy, there is an expectation that these discoveries will be followed by improved therapies and combination treatments leading to greater efficacy in ameliorating the clinical

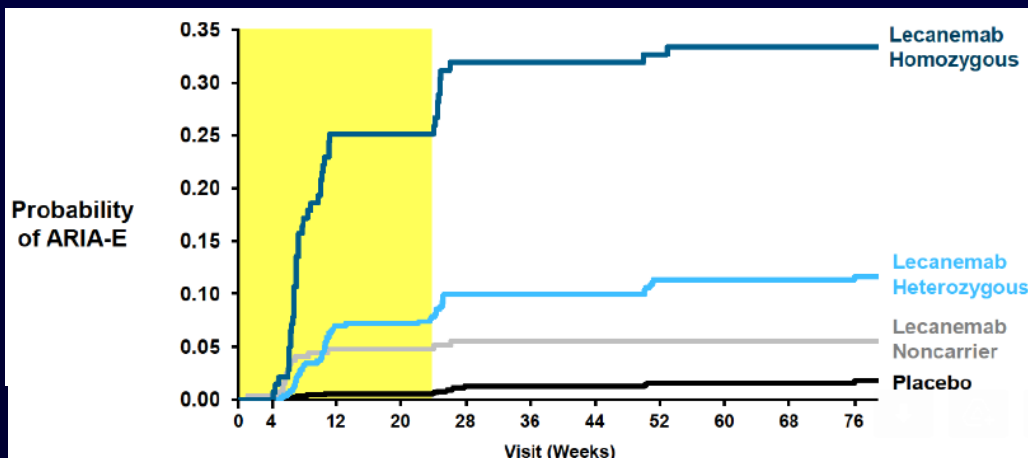
# Personalizace - ještě lepší výsledky

## Stratifikace podle ApoE4

### Účinnost:

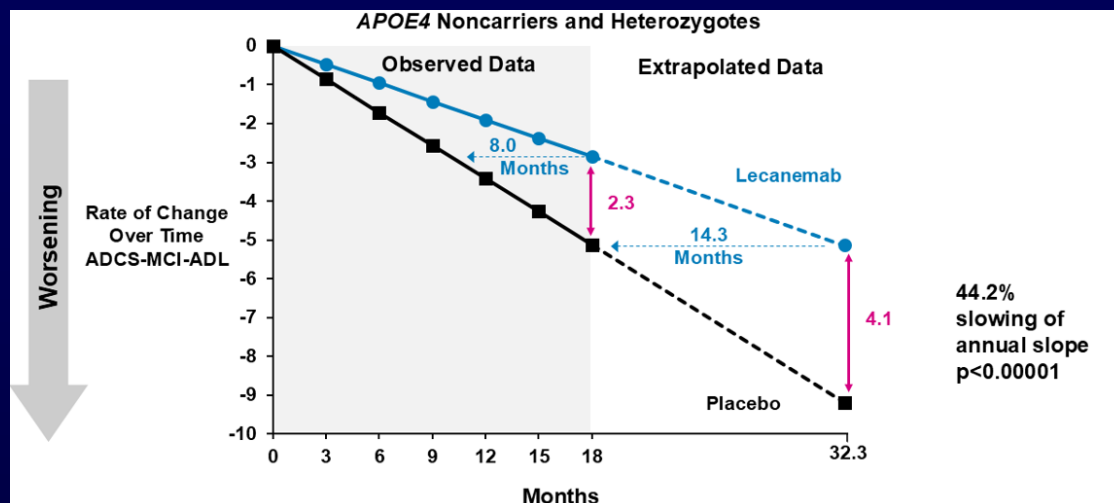


### Bezpečnost:

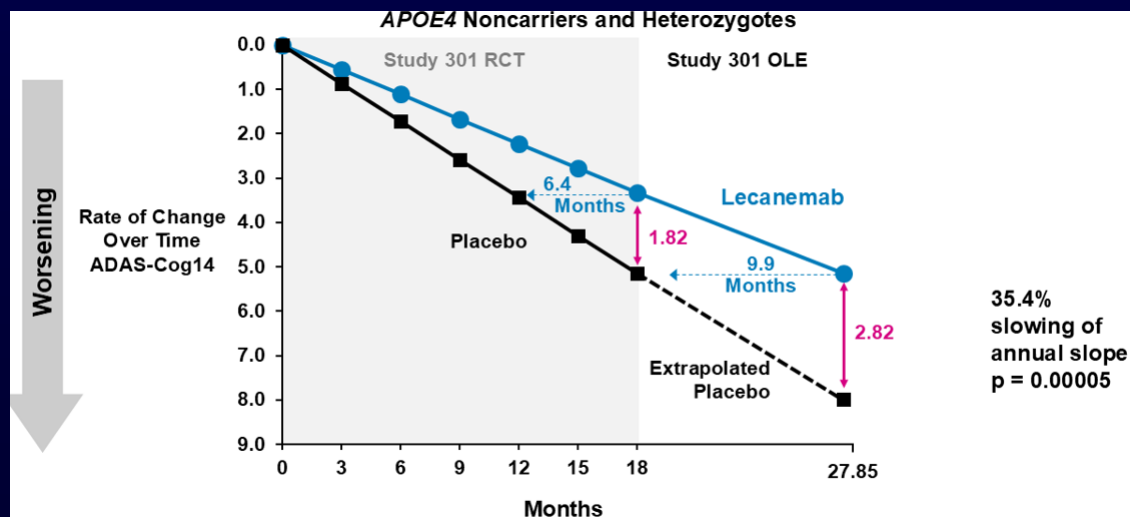


# MCI – lepší účinnost

Soběstačnost:



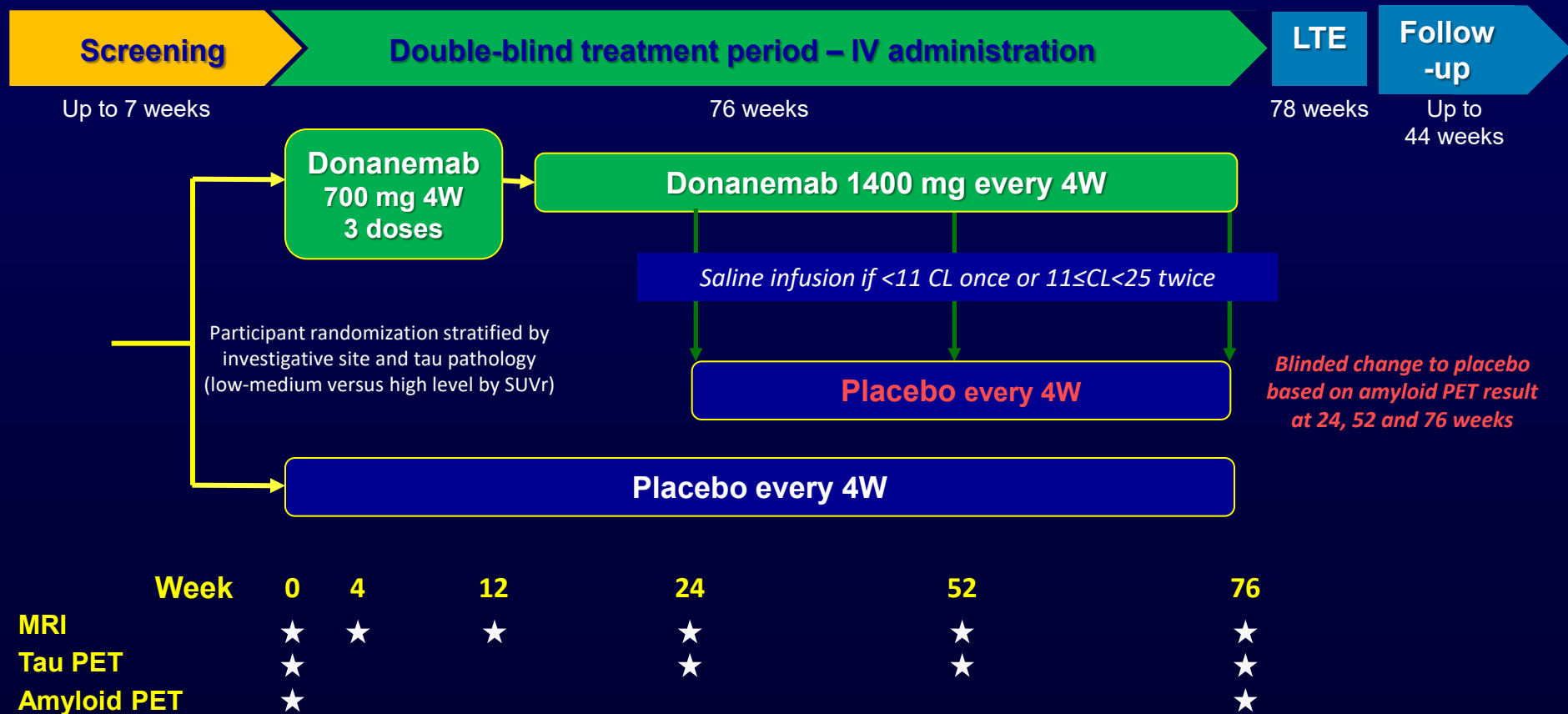
Kognice:



x 28%  
u všech

# Donanemab

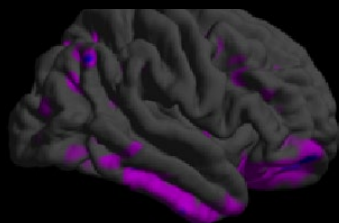
## — studie TRAILBLAZER-ALZ 2



Abbreviations: CL=centiloid unit; IV=intravenous; LTE=long term extension; PET=positron emission tomography; Q4W=every 4 weeks; SUVR=standardized uptake value ratio

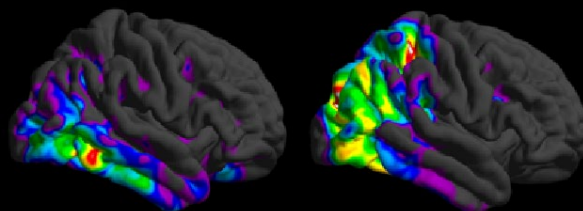
# Studie donanemab – tau podskupiny

Bez tau patologie a  
velmi nízké tau  
- nebyli zařazeni



**Study Powered to Test  
Low-medium Tau Population**  
(same as TRAILBLAZER-ALZ Phase 2)

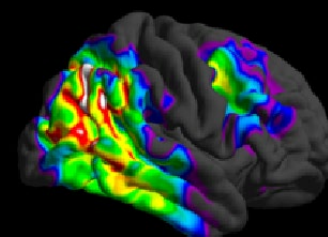
Nízké – střední tau



$1.10 < \text{Tau SUVr} \leq 1.46^*$

**High tau allowed to test  
combined population  
(low-medium + high tau)**

Vysoké tau



$\text{Tau SUVr} > 1.46$

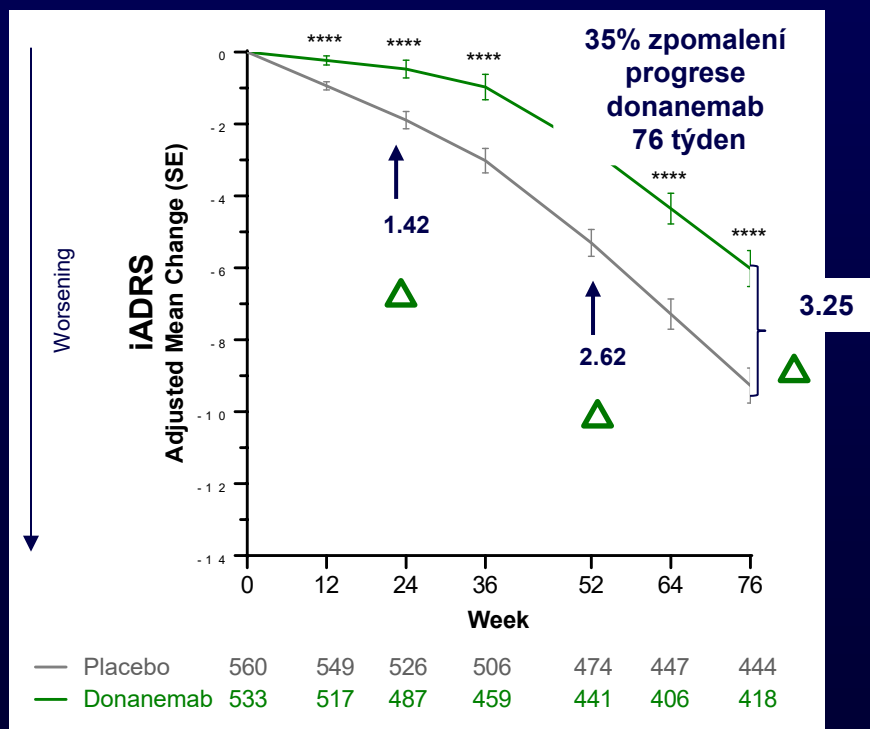
Copyright (C) 2023 Eli Lilly and Company. All rights reserved

Abbreviations: MUBADA=multi-block barycentric discriminant analysis; PERSI=parametric estimation of reference signal intensity; SUVr=standardized uptake value ratio based on MUBADA region with PERSI reference region

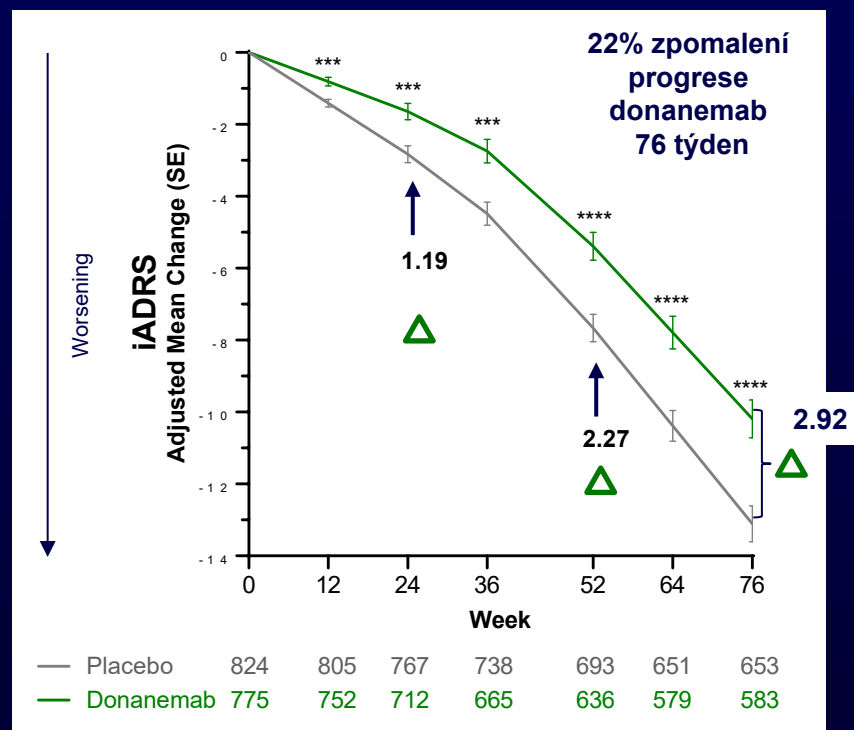
# Primární cíl donanemab: iADRS

iADRS = Integrated Alzheimer's Disease Rating Scale

Low-medium Tau



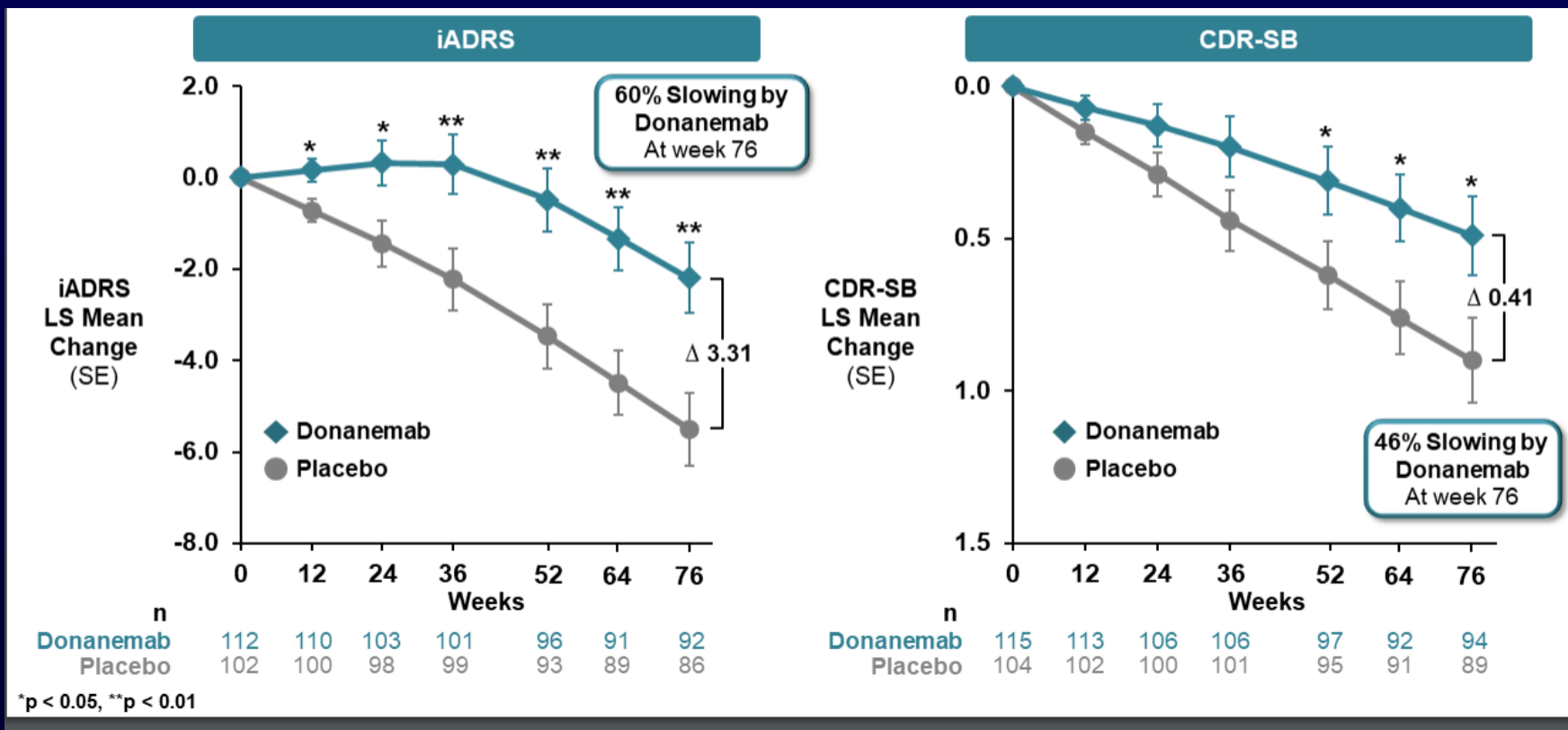
Všichni pacienti



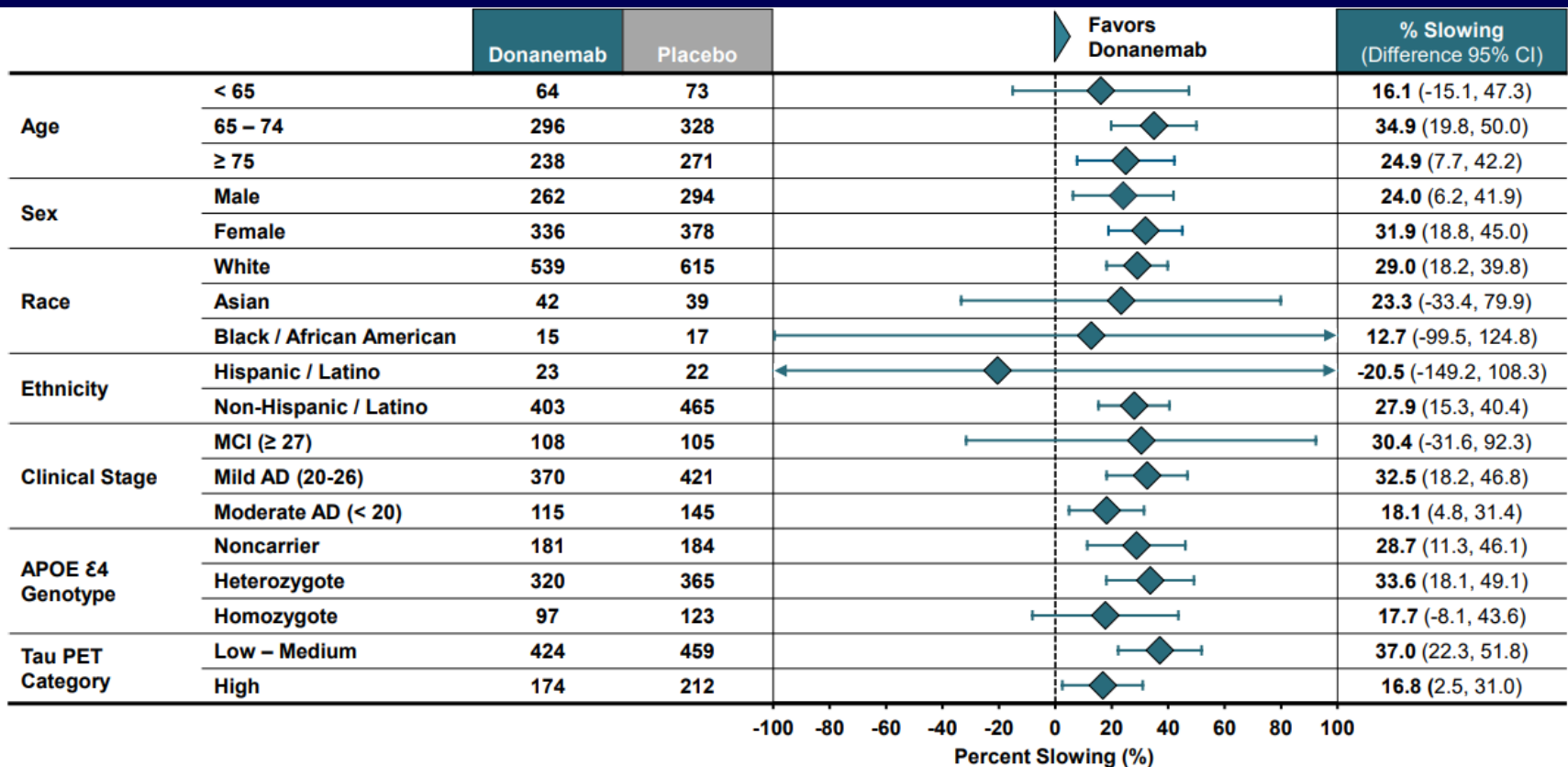
**U obou skupin je efekt a zvětšuje se s časem**

# Časnější onemocnění – větší efekt

Low-medium Tau + MCI = časnější stádium AN

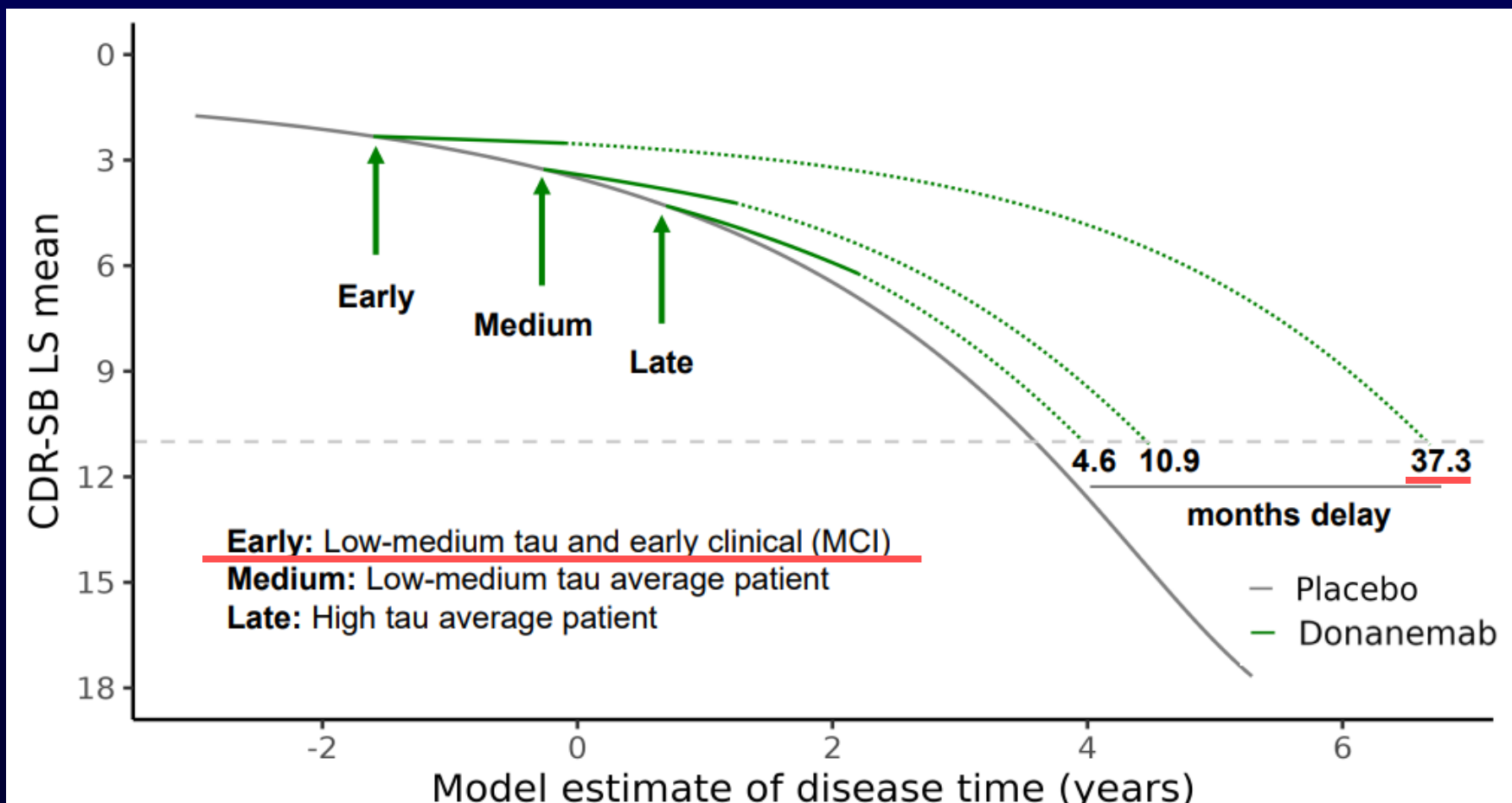


# Donanemab – efekt u podskupin soběstačnost (CDR-SB)



# Získání cenného času....

Personalizace – nízký, střední a vysoký tau protein



# Délka léčby – „treat to clear“

- Kontrolní amyloid PET by měl smysl
- 52% **dokončilo léčbu v 12 ( 72% v 18) měsíci** = bA vyčištěn

*Kisunla Limited-Duration Treatment Examples*

| Length of Treatment    | 6 months | 12 months | 18 months |
|------------------------|----------|-----------|-----------|
| 30-Minute Infusions    | 6        | 13        | 19        |
| Course of Therapy Cost | \$12,522 | \$32,000  | \$48,696  |

ADCS-iADL=Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living Inventory; CDR-GS=Clinical Dementia Rating Scale Global Score; CDR-SB=Clinical Dementia Rating Scale Sum of Boxes; HR=Hazard Ratio; PBO=Placebo.

<https://investor.lilly.com/news-releases/news-release-details/lillys-donanemab-significantly-slowed-cognitive-and-functional> (Accessed May 2023).

# „Americké SPC Leqembi“

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LEQEMBI™ safely and effectively. See full prescribing information for LEQEMBI™.

**LEQEMBI™ (lecanemab-irmb) injection, for intravenous use**  
**Initial U.S. Approval: 2023**

## INDICATIONS AND USAGE

LEQEMBI is an amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease. Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with LEQEMBI. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial. (1)

## DOSAGE AND ADMINISTRATION

- Confirm the presence of amyloid beta pathology prior to initiating treatment. (2.1)
- The recommended dosage is 10 mg/kg that must be diluted then administered as an intravenous infusion over approximately one hour, once every two weeks. (2.2)
- Obtain a recent (within one year) brain MRI prior to initiating treatment to evaluate for pre-existing Amyloid Related Imaging Abnormalities (ARIA). (2.3, 5.1)
- Obtain an MRI prior to the 5<sup>th</sup>, 7<sup>th</sup>, and 14<sup>th</sup> infusions. If radiographically observed ARIA occurs, treatment recommendations are based on type, severity, and presence of symptoms. (2.3, 5.1)
- Dilution in 250 mL of 0.9% Sodium Chloride Injection, USP, is required prior to administration. (2.4)
- Administer as an intravenous infusion over approximately one hour via a terminal low-protein binding 0.2 micron in-line filter. (2.5)

## DOSAGE FORMS AND STRENGTHS

Injection:

- 500 mg/5 mL (100 mg/mL) solution in a single-dose vial (3)
- 200 mg/2 mL (100 mg/mL) solution in a single-dose vial (3)

## CONTRAINDICATIONS

None. (4)

## WARNINGS AND PRECAUTIONS

- **Amyloid Related Imaging Abnormalities (ARIA):** Enhanced clinical vigilance for ARIA is recommended during the first 14 weeks of treatment with LEQEMBI. Risk of ARIA, including symptomatic ARIA, was increased in apolipoprotein E ε4 homozygotes compared to heterozygotes and noncarriers. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including MRI scanning if indicated. (2.3, 5.1)
- **Infusion-Related Reactions:** The infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy administered as clinically indicated. Consider pre-medication at subsequent dosing with antihistamines, non-steroidal anti-inflammatory drugs, or corticosteroids. (5.2)

## ADVERSE REACTIONS

Most common adverse reactions (at approximately 10% and higher incidence compared to placebo): infusion-related reactions, headache, and ARIA-edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai Inc. at 1-888-274-2378 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 1/2023

# Indikace preklinická AN?

- Ukládání A $\beta$  začíná 20 let před klinickými příznaky
- Klinické příznaky = tau patologie/atrofie
- lecanemab + donanemab:
  - cílí na různé formy A $\beta$
  - redukce A $\beta$  na PET v závislosti na dávce
- Hypotéza: odstranění A $\beta$  v nejčasnějším stádiu AN, před tím než nastane ireverzibilní neurodegenerace = nejlepší příležitost zpomalit nebo zastavit progresi AN a předejít tak rozvoji kognitivního deficitu

# Indikace preklinická AN?



## Safety and efficacy of long-term gantenerumab treatment in dominantly inherited Alzheimer's disease: an open-label extension of the phase 2/3 multicentre, randomised, double-blind, placebo-controlled platform DIAN-TU trial

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### Summary

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\*Members of the Trials Unit listed in the appendix

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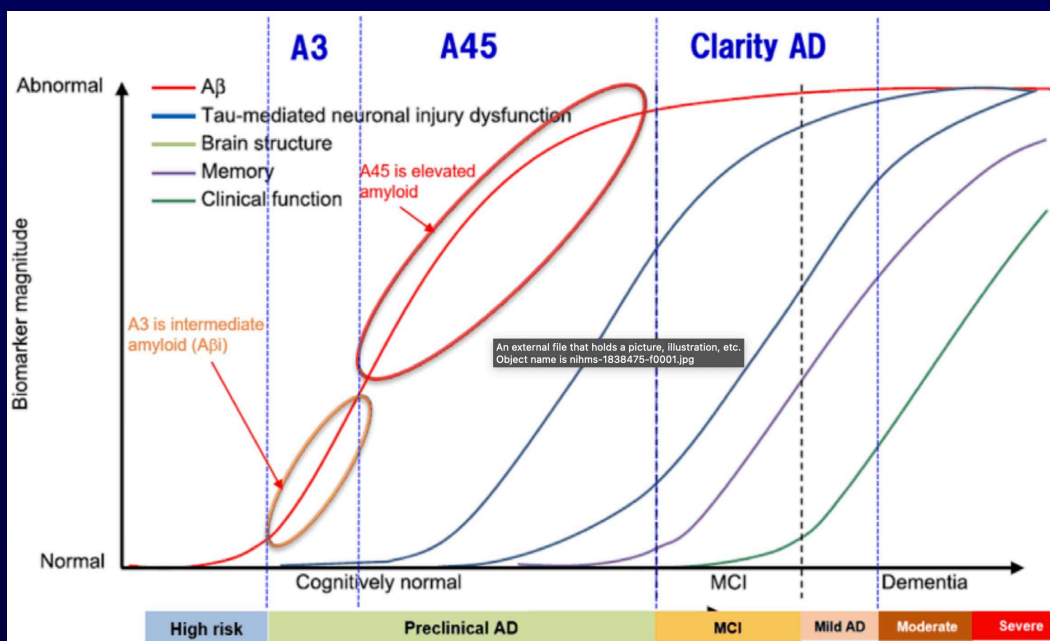
P Delmar PhD, G A Kerchner MD,

**Background** Amyloid plaque removal by monoclonal antibody therapies slows clinical progression in symptomatic Alzheimer's disease; however, the potential for delaying the onset of clinical symptoms in asymptomatic people is unknown. The Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) is an ongoing platform trial assessing the safety and efficacy of multiple investigational products in participants with dominantly inherited Alzheimer's disease (DIAD). Based on findings of amyloid removal and downstream biological effects from the gantenerumab group of the platform trial, we continued a 3-year open-label extension (OLE) study to assess the safety and efficacy of long-term treatment with high doses of gantenerumab.

**Methods** The randomised, placebo-controlled, double-blind, phase 2/3 multi-arm trial (DIAN-TU-001) assessed solanezumab or gantenerumab versus placebo in participants who were between 15 years before and 10 years after their estimated years to symptom onset and who had a Clinical Dementia Rating (CDR) global score of 0 (cognitively normal) to 1 (mild dementia). This study was followed by an OLE study of gantenerumab treatment, conducted at 18 study sites in Australia, Canada, France, Ireland, Puerto Rico, Spain, the UK, and the USA. For inclusion in the OLE, participants at risk for DIAD had participated in the double-blind period of DIAN-TU-001 and were required to know their mutation status. We investigated increasing doses of subcutaneous gantenerumab up to 1500 mg every 2 weeks. Due to the lack of a regulatory path for gantenerumab, the study was stopped early after a prespecified interim analysis (when most participants had completed 2 years of treatment) of the clinical measure CDR-Sum of Boxes (CDR-SB). The primary outcome for the final analysis was the amyloid plaque measure <sup>11</sup>C-Pittsburgh compound-B positron emission tomography (PiB-PET) standardised uptake value ratio (SUVR [PiB-PET SUVR]) at 3 years, assessed in the modified intention-to-treat group (mITT; defined as participants who received any gantenerumab treatment post-OLE baseline, had at least one PiB-PET SUVR assessment before gantenerumab treatment, and a post-baseline assessment). All participants who received at least one dose of study drug in the OLE were included in the safety analysis. DIAN-TU-001 (NCT01760005) and the OLE (NCT06424236) are registered with ClinicalTrials.gov.

# AHEAD 3-45 study

## - lecanemab u preklinické AN



(výsledky 2027)

- Multicentrická, placebem kontrolovaná, dvojité zaslepená, paralelní skupiny
- A3 trial – 448 „pacientů“ bez kognitivního deficitu!  
amyloid pozitivní 20-40 centiloidů (časná preklinická), lecanemab 4 roky
- A45 trial - 1173 „pacientů“ bez kognitivního deficitu!  
amyloid pozitivní > 40 centiloidů (pozdí preklinická) 10 mg/kg, 4 roky

( The AHEAD 3–45 Study: Design of a prevention trial for Alzheimer’s disease; Rafii et al., 2023)

# TRAILBLAZER-ALZ 3 study - donanemab u preklinické AN

(výsledky 2027)

- Multicenter, randomized, double-blind, placebo-controlled Phase 3 trial\*
- Decentralized study design

## Study Population

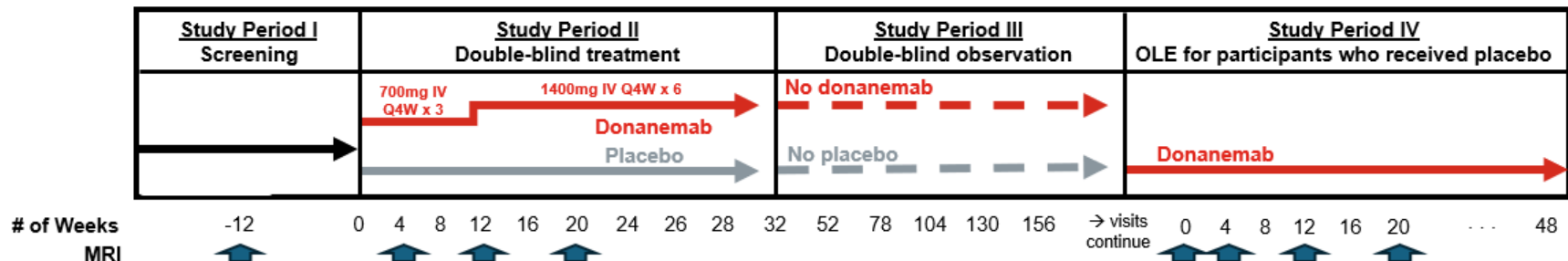
- Cognitively unimpaired + AD pathology (preclinical AD)
- Study partners required
- USA and Japan

## Key Inclusion Criteria

- Age 55-80†
- TICS-m score  $\geq 35$ ‡
- Eligible plasma P-tau217 assay result

## Key Exclusion Criteria

- Other significant neurodegenerative disease
- Current or previous use of prescription medications to treat MCI or AD



\* NCT05026866

† Screening of ages 55-64 was stopped after one year

‡ CDR-GS not used for eligibility

Abbreviations: AD = Alzheimer's disease; CDR-GS = Clinical Dementia Rating Scale – Global Score; MCI = mild cognitive impairment

# Demence je jen špička ledovce

|                | Normální kognice                   | Zhoršení paměti                       | Demence při Alzheimerově nemoci |           |           |                       |
|----------------|------------------------------------|---------------------------------------|---------------------------------|-----------|-----------|-----------------------|
|                | V riziku - Amyloid pozitivní (50+) | Amnestic MCI, Amyloid pozitivní (60+) | mírná                           | střední   | těžká     | Celkem demence při AN |
| <b>US</b>      | 24,000,000                         | 7,100,000                             | 1,425,000                       | 1,650,000 | 2,325,000 | 5,400,000             |
| <b>Germany</b> | 6,100,000                          | 1,800,000                             | 362,000                         | 419,000   | 590,000   | 1,370,000             |
| <b>Spain</b>   | 3,100,000                          | 1,000,000                             | 183,000                         | 212,000   | 298,000   | 700,000               |
| <b>France</b>  | 4,400,000                          | 1,300,000                             | 258,000                         | 298,000   | 420,000   | 980,000               |
| <b>Italy</b>   | 4,500,000                          | 1,400,000                             | 268,000                         | 310,000   | 437,000   | 1,020,000             |
| <b>UK</b>      | 4,200,000                          | 1,300,000                             | 246,000                         | 285,000   | 401,000   | 940,000               |

# Závěr

- Prevence (pohyb, strava, kognitivní, více v Terrapinu)
- Inhibitory acetylcholinesterázy + memantine + EGb761
- BPSD
- Biologická léčba:
  - Bezpečnost – ARIA ( ApoE4)
  - Účinnost - zpomalení progresu
    - 35% v jiných oborech považováno za významné
- Personalizovaná medicína - ještě lepší efekt
  - ApoE4, nízké a střední tau, MCI
  - preklinická AN???
  - starší? muži x ženy?