TOP 5 GERIATRIC MEDICINE ARTICLES OF 2023

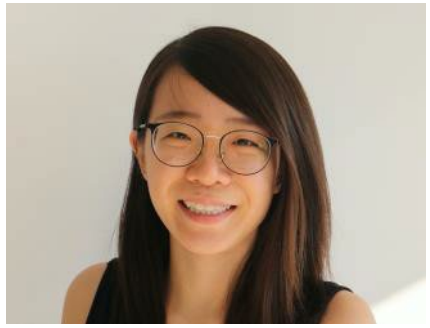
Carolyn Tan, Natasha Lane, Barry Goldlist

2023 Toronto Geriatrics Update Course
Friday November 10th
11:50 AM – 12:40 PM EST

Sinai Health | Healthy Ageing and Geriatrics
UHN Toronto General Toronto Western Princess Margaret Toronto Rehab Michener Institute

TOP 5 GERIATRIC MEDICINE ARTICLES OF 2023

Natasha Lane
PGY4 in Geriatric Medicine



Carolyn Tan
PGY5 in Geriatric Medicine

Barry Goldlist
Geriatrician

CONFLICT OF INTEREST

Natasha Lane-none

Carolyn Tan-none

Barry Goldlist-none

LEARNING OBJECTIVES

- **Be informed of the top geriatric-related articles of 2023**
- **Be aware of the latest evidence regarding the care of patients in primary, community and hospital settings**
- **Appreciate which ‘Take Away Points’ from our presentation that you can apply to your own practice**

Circulation

FREE ACCESS

RESEARCH ARTICLE

PDF/EPUB

Tools Share

Safety of Switching from a Vitamin K Antagonist to a Non-Vitamin K Antagonist Oral Anticoagulant in Frail Older Patients with Atrial Fibrillation: Results of the FRAIL-AF Randomized Controlled Trial

Linda P.T. Joosten, Sander van Doorn, Peter M. van de Ven, Bart T.G. Köhlen, Melchior C. Nierman, Huiberdina L. Koek, Martin E.W. Hemels, Menno V. Huisman, Marieke Kruip, Laura M. Faber, Nynke M. Wiersma, Wim F. Buding, Rob Fijnheer, Henk J. Adriaansen, Kit C. Roes, Arno W. Hoes, Frans H. Rutten and Geert-Jan Geersing

Originally published 27 Aug 2023 | https://doi.org/10.1161/CIRCULATIONAHA.123.066485 | Circulation. 2023;0

Background

- Ample evidence of ↓ risk bleeding, ↔ or ↓ risk thromboembolism risk when DOAC vs VKA prescribed for incident atrial fibrillation.[1]
- Canadian guidelines extend this evidence to suggest switching people on VKA to DOAC.[2]
- Risk/benefit of switching in frail older adults unknown.

1. Grymonprez et al. Front Pharmacol. 2020; 11:583311.
2. Andrade et al. Can J Cardio 2020; 36(12): 1847-1948

Objective

To assess whether frail older adults with atrial fibrillation on a vitamin K antagonist (VKA) should be switched to a direct oral anticoagulant (DOAC).

Methods: pragmatic RCT

- **Population:** ≥75 years old, Netherlands thrombosis pt, Groningen Frailty Index ≥3, willing to switch VKA → DOAC.

- **Intervention:** Switch from INR-guided VKA treatment to DOAC

- **Primary outcome**
  - Major or clinically relevant non-major bleeding complication (whichever 1st) in 1-year post-randomization

- **Secondary outcomes**
  - thromboembolic events, minor bleeding, composite of ischemic and haemorrhagic stroke

- **Analysis:** intention-to-treat, Cox proportional hazards model

Results

- 1,330 frail older adults with afib + OAC indication randomized to continue VKA (n=662) vs DOAC switch (668)

- Mean age 83 years (SD 5.1), Median GFI 4 (frail), TTR 65.3-74.0%

Characteristic	DOAC Switch group	Continue VKA group
Females	41.4%	36.2%
HTN	55.1%	50.8%
History of major bleeding	15.9%	13.3%
History of thromboembolism	21.0%	17.7%

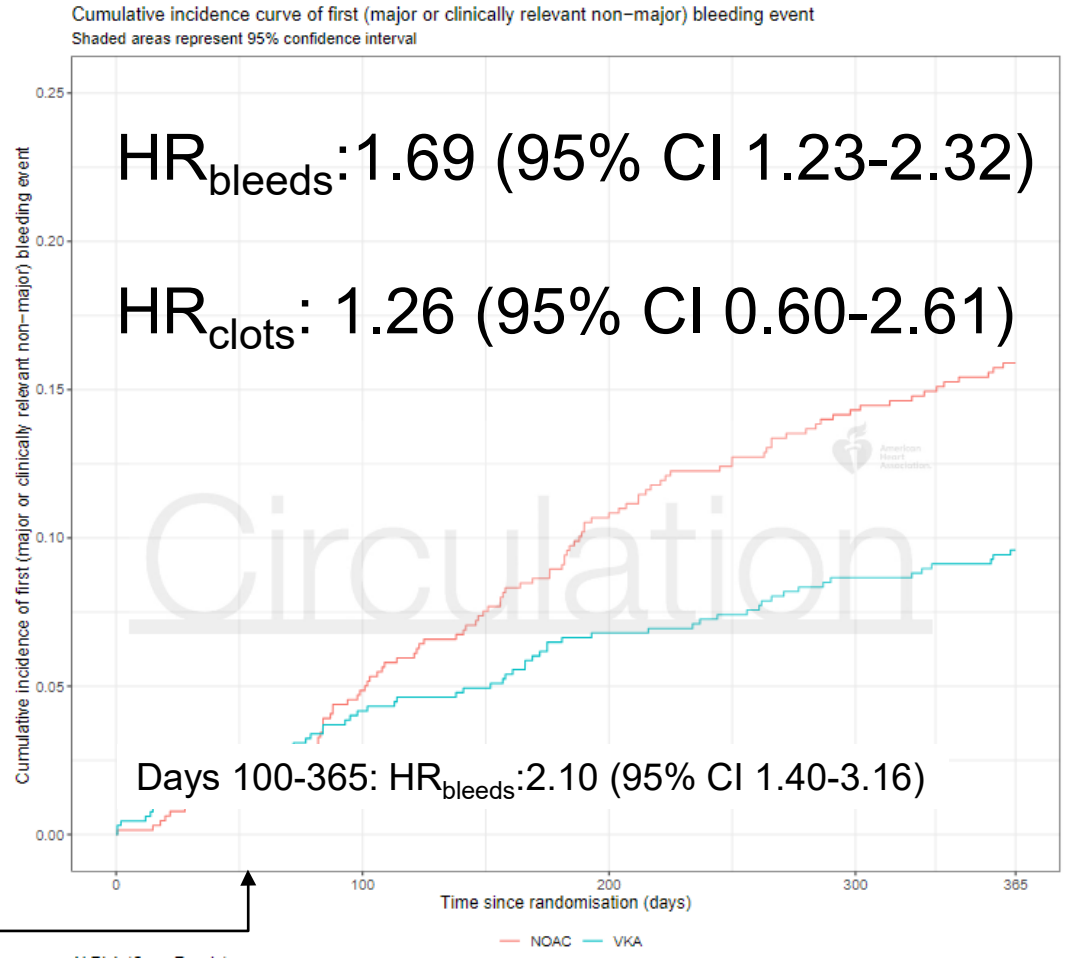
More bleeding with switch!

90 pts died during mean 344 days follow-up.

$HR_{CRNM\ bleeding}$ 1.77 (95%CI 1.24-2.52)

$HR_{MajorBleed}$ 1.52 (95%CI 0.81-2.87)

101 (15.3%) of switch group had outcome, vs 62 (9.4%) of control group. **NNH = 17**



Median 52 (IQR 35-72) days between randomization and DOAC start

Results

- ↑ bleeding across subgroups of DOAC, age, frailty, GFR strata except dabigatran, edoxaban, females, eGFR <49

- Most of increased bleeding happened in GI, skin, urogenital sites
    - 50% of switch patients were switched to rivaroxaban

- HR 1.26 (95% CI 0.60-2.61) for thromboembolic events in intervention vs control arm

Discussion

Strengths

- RCT with 89-92% intervention adherence in both arms
- Used validated frailty score (GFI) to identify participants
- Population generalizable to patients we routinely see in outpatient setting

Cautions

- Design selects for people tolerating VKA
- Some baseline differences not adjusted for in analysis
- Bias from unblinded randomization, intervention assignment

Bottom Line

If it’s not broken, don’t fix it.

If frail older patient struggling to keep time in therapeutic range on VKA, consider swap to DOAC (not rivaroxaban).

JAMA Internal Medicine | Original Investigation

Development and External Validation of a Mortality Prediction Model for Community-Dwelling Older Adults With Dementia

W. James Deardorff, MD; Deborah E. Barnes, PhD, MPH; Sun Y. Jeon, PhD; W. John Boscardin, PhD; Kenneth M. Langa, MD, PhD; Kenneth E. Covinsky, MD, MPH; Susan L. Mitchell, MD, MPH; Elizabeth L. Whitlock, MD, MS; Alexander K. Smith, MD, MS, MPH; Sei J. Lee, MD, MAS

JAMA IM. 2022; 182(11): 1161-1170.

Background

- Prognosticating survival in people with dementia is important and challenging

- A well-validated and easy to apply prognostic model for mortality in community-dwelling older adults with dementia did not exist prior to this study[1]

1. J Alzheimer's Disease 2021; 80(1):103-111.
JAMA IM. 2022; 182(11): 1161-1170.

Objective

- To develop and externally validate a mortality prediction model in nationally representative cohorts of community-dwelling older adults with dementia in the US

JAMA IM. 2022; 182(11): 1161-1170.

Methods

- **Cohorts**
  - Community-dwelling, > 65, probable dementia
  - Derivation cohort (n = 4267)
    - Health and Retirement Study (HRS)
  - Validation cohort (n = 2404)
    - National health and Aging Trends Study (NHATS)

- **Primary Outcome**
  - All-cause mortality

- **Methods**
  - Cox proportional hazards model

JAMA IM. 2022; 182(11): 1161-1170.

Results

- Mean age 82
- ¼ to 1/3 live alone
- 1/3 with ≥1 ADL dependence

- Comparable burden chronic disease to Ontario cohort persons with dementia[1]

1. PLOS Med 2017; 7;14(3):e1002249.
JAMA IM. 2022; 182(11): 1161-1170.

Results

- Variables included in final model
  - Age, sex
  - BMI
  - smoking status
  - ADL/IADL dependence count
  - Difficulty walking several blocks
  - Regular vigorous physical activity
  - Diabetes
  - heart/lung disease
  - non-skin cancer

JAMA IM. 2022; 182(11): 1161-1170. PLOS Med 2017; 7;14(3):e1002249.

Results

- Discrimination, Area Under Curve (AUC)
  - 0.76 at 1 year
  - 0.84 at 10 years
- Accuracy
  - Integrated Brier score 0.1
- Calibration between predicted and expected outcomes good

JAMA IM. 2022; 182(11): 1161-1170.

Discussion

- Strengths
  - Based on variables most of us would have in our consults
    - does not require cognitive testing
  - Discrimination, accuracy, calibration on par with other heavily used predictive scores

- Cautions
  - Dementia etiology not included
  - Tailor prognostication information to patient and their family

JAMA IM. 2022; 182(11): 1161-1170.

JAMA. 2001; 286(2):180-187.

Bottom Line

The mortality prediction tool for persons with dementia is as accurate a prediction score as others we routinely use in clinical practice – practice changing - start using this today at eprognosis.com

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Haloperidol for the Treatment of Delirium in ICU Patients

N.C. Andersen-Ranberg, L.M. Poulsen, A. Perner, J. Wetterslev, S. Estrup, J. Hästbacka, M. Morgan, G. Citerio, J. Caballero, T. Lange, M.-B.N. Kjær, B.H. Ebdrup, J. Engstrøm, M.H. Olsen, M. Oxenbøll Collet, C.B. Mortensen, S.-O. Weber, A.S. Andreasen, M.H. Bestle, B. Uslu, H. Scharling Pedersen, L. Gramstrup Nielsen, H.C. Toft Boesen, J.V. Jensen, L. Nebrich, K. La Cour, J. Laigaard, C. Haurum, M.W. Olesen, C. Overgaard-Steensen, B. Westergaard, B. Brand, G. Kingo Vesterlund, P. Thornberg Kyhnauv, V.S. Mikkelsen, S. Hyttel-Sørensen, I. de Haas, S.R. Aagaard, L.O. Nielsen, A.S. Eriksen, B.S. Rasmussen, H. Brix, T. Hildebrandt, M. Schønemann-Lund, H. Fjeldsøe-Nielsen, A.-M. Kuivalainen, and O. Mathiesen, for the AID-ICU Trial Group*

DECEMBER 29, 2022

N Engl J Med. 2022; 387:2425-35

Background

- Delirium affects about 70% of older adults in the ICU
- Associated with increased mortality, LOS, functional decline, long-term cognitive impairment, and institutionalization
- Haloperidol is not supported by clinical practice guidelines due to lack of evidence

J Am Geriatr Soc 2003; 51(5):591-8
Arch Intern Med 2007; 167(15):1629
Acta Anaesthesiol Scand 2019;64(2):254-66
Semin Respir Crit Care Med 2001;22(02):115-26

Methods

- **Design:** multicenter, double-blind, randomized, placebo-controlled
- **Population:** adults with delirium (CAM-ICU or ICDSC) in the ICU
- **Intervention:** haloperidol 2.5mg IV TID and PRN (daily max 20mg) vs. placebo

N Engl J Med. 2022; 387:2425-35

CAM-ICU = Confusion Assessment Method for ICU
ICDSC = Intensive Care Delirium Screening Checklist

Methods

- **Primary outcome**
  - Number of days alive and out of hospital at 90 days after randomization

- **Secondary outcomes**
  - Serious adverse reactions
  - Use of rescue medications
  - # of days without delirium or coma
  - # of days without mechanical ventilation

- **Analysis:** intention-to-treat

N Engl J Med. 2022; 387:2425-35

Results

- 1000 adults aged 18+ with delirium in the ICU
- 16 centers in Europe

- **Average participant**
  - Age 70, male
  - 66% medical admission
  - 55% hypoactive delirium
  - 63% on mechanical ventilation
  - 52% on vasopressors or inotropes
  - < 1% with neurodegenerative disease

N Engl J Med. 2022; 387:2425-35

Results

Outcome	Haloperidol	Placebo	Adjusted Absolute Difference (95% or 99% CI)†	Adjusted Relative Risk (95% or 99% CI)†	P Value
Primary outcome					
Days alive and out of hospital at 90 days — raw mean no. (95% CI)‡	35.8 (32.9 to 38.6)	32.9 (29.9 to 35.8)	2.9 (–1.2 to 7.0)§	NC	0.22¶
Death — no./total no. (%)‖	182/501 (36.3)	210/485 (43.3)	–6.9 (–13.0 to –0.6)**	0.84 (0.72 to 0.98)	
Length of hospital stay — raw mean no. of days (95% CI)††	28.8 (26.7 to 30.8)	26.4 (24.4 to 28.5)	2.3 (–0.6 to 5.1)§	NC	

N Engl J Med. 2022; 387:2425-35

Results

- No heterogeneity by:
  - Type of delirium
  - Age (< 69, ≥ 69)
  - Sex
  - Admission type
  - Delirium risk factors
  - Predicted 90-day mortality

- Secondary outcomes were similar in both groups

N Engl J Med. 2022; 387:2425-35

Discussion

- Large, well-conducted RCT that addressed an area of great clinical need
- Haloperidol was given standing for both hypoactive and hyperactive delirium
- Very low rates of underlying neurodegenerative disease
- Haloperidol dose differs from our typical practice

N Engl J Med. 2022; 387:2425-35

Bottom Line

Use of haloperidol for patients with delirium in the ICU should continue to be an individualized decision

Received: 1 November 2021 | Revised: 8 March 2022 | Accepted: 12 March 2022

DOI: 10.1111/jgs.17788

Journal of the
American Geriatrics Society

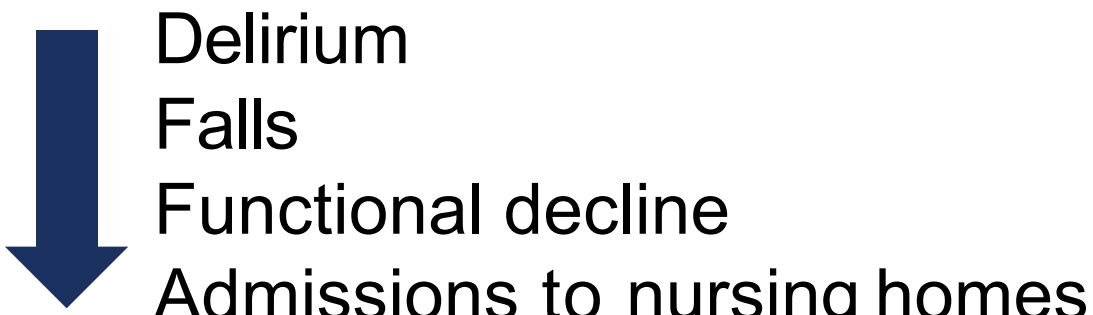
Patient outcomes related to receiving care on a dedicated Acute Care for Elders (ACE) unit versus with an ACE order set

Richard E. Norman MD, MASc, MSc[1,2] | Samir K. Sinha MD, DPhil[1,2]

J Am Geriatr Soc. 2022; 70:2101-06

Background

- Older adults are at increased risk of adverse outcomes during hospitalization which contribute to further loss of independence



- # of patients who could benefit often exceeds ACE unit capacity

Age Ageing 2022; 51:1-11 J Am Geriatr Soc. 2012; 60(12):2237-45 J Am Geriatr Soc. 2022; 70:2101-06

Objective

- Protocolized order sets have been developed to provide patients bed-spaced on non-ACE units with several aspects of the ACE model of care

- Is the ACE model equally effective when applied this way?

J Am Geriatr Soc. 2022; 70:2101-06

Methods

- **Design:** retrospective cohort of ACE-eligible patients aged 65+
- **Location:** Mount Sinai Hospital, Toronto
- **Intervention:** admission to 28-bed ACE unit vs. bed-spaced with protocolized ACE order set

J Am Geriatr Soc. 2022; 70:2101-06

Methods

- **Primary outcomes**
  - Discharge disposition (home or other location)
  - In-hospital mortality

- **Data collection:** over 5 years, ending in 2018

J Am Geriatr Soc. 2022; 70:2101-06

Methods

Intervention	ACE Unit	ACE Order Set (Bed-Spaced)
Dedicated daily interdisciplinary rounds on geriatric-specific issues	Yes	No
Physical Environment		
Prominent clocks and calendars in every room	Yes	No
High contrast environment, enhanced lighting	Yes	No
Patient Care		
Supervision by geriatric nursing practitioner	Yes	No
Specialized geriatric nursing training	Yes	No
Specialized nursing training in prevention and management of delirium	Yes	No
Specialized continence training	Yes	No

J Am Geriatr Soc. 2022; 70:2101-06

Results

Characteristic	ACE Unit ($n = 1499$)	Bed-Spaced ($n = 1547$)
Age in years (mean)	**83.5**	**82.6**
Sex, No. (%)		
Male	589 (39.3)	608 (39.3)
Female	910 (60.7)	939 (60.7)
Resource use as defined by RIW		
Median	1.06	0.97
Mean	1.48	1.35
Length of stay, days		
Median	5.9	4.8
Mean	8.4	7.3
Discharge diagnosis, No. (%)		
Functional decline	116 (7.7)	105 (6.8)
Pneumonia	92 (6.1)	103 (6.7)
Congestive heart failure	86 (5.7)	85 (5.5)

J Am Geriatr Soc. 2022; 70:2101-06

Results

- Patients on the ACE unit were more likely to be discharged home
  - **OR 1.31**, 95% CI 1.12-1.54, p = 0.001

- And less likely to die in hospital
  - **OR 0.70**, 95% CI 0.51-0.95, p = 0.02

J Am Geriatr Soc. 2022; 70:2101-06

Results

- Post-hoc analysis adjusted for potential case mix differences
- Patients on the ACE unit still more likely to be discharged home
  - **OR 1.23**, 95% CI 1.02-1.50, p = 0.033
- Mortality benefit no longer present
  - **OR 0.89**, 95% CI 0.60-1.33, p = 0.63

J Am Geriatr Soc. 2022; 70:2101-06

Cautions

- Single institution
- Non-randomized study
- Fidelity to ACE interventions was not tracked

J Am Geriatr Soc. 2022; 70:2101-06

Cautions

- Impact of bed-spacing to different floors and surgical units
- No comparison to usual care
- Readmission and cost data would be helpful

J Am Geriatr Soc. 2022; 70:2101-06

Bottom Line

ACE units reflect a synergy of staff expertise, resources, and a culture that values caring for older adults

The whole is likely greater than the sum of its parts

AMSTERDAM 1998

Highlights of Alzheimer Society Meeting 1998

- Great bicycle tour through the countryside
- Introduction of cholinesterase inhibitors (limitations understood)
- ***We thought this was going to be the start of incredible research breakthroughs, but we were wrong***
- Many of the major investigators presenting were ferried around town by large Mercedes sedans paid for by pharmaceutical companies (I made a vow never again to accept personal remuneration or rewards from drug companies)

AMSTERDAM 2023

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

- Published online July 17, 2023 in JAMA
- Huge news coverage
- Is this a game changer?

A REMINDER ABOUT PREVIOUS STUDIES

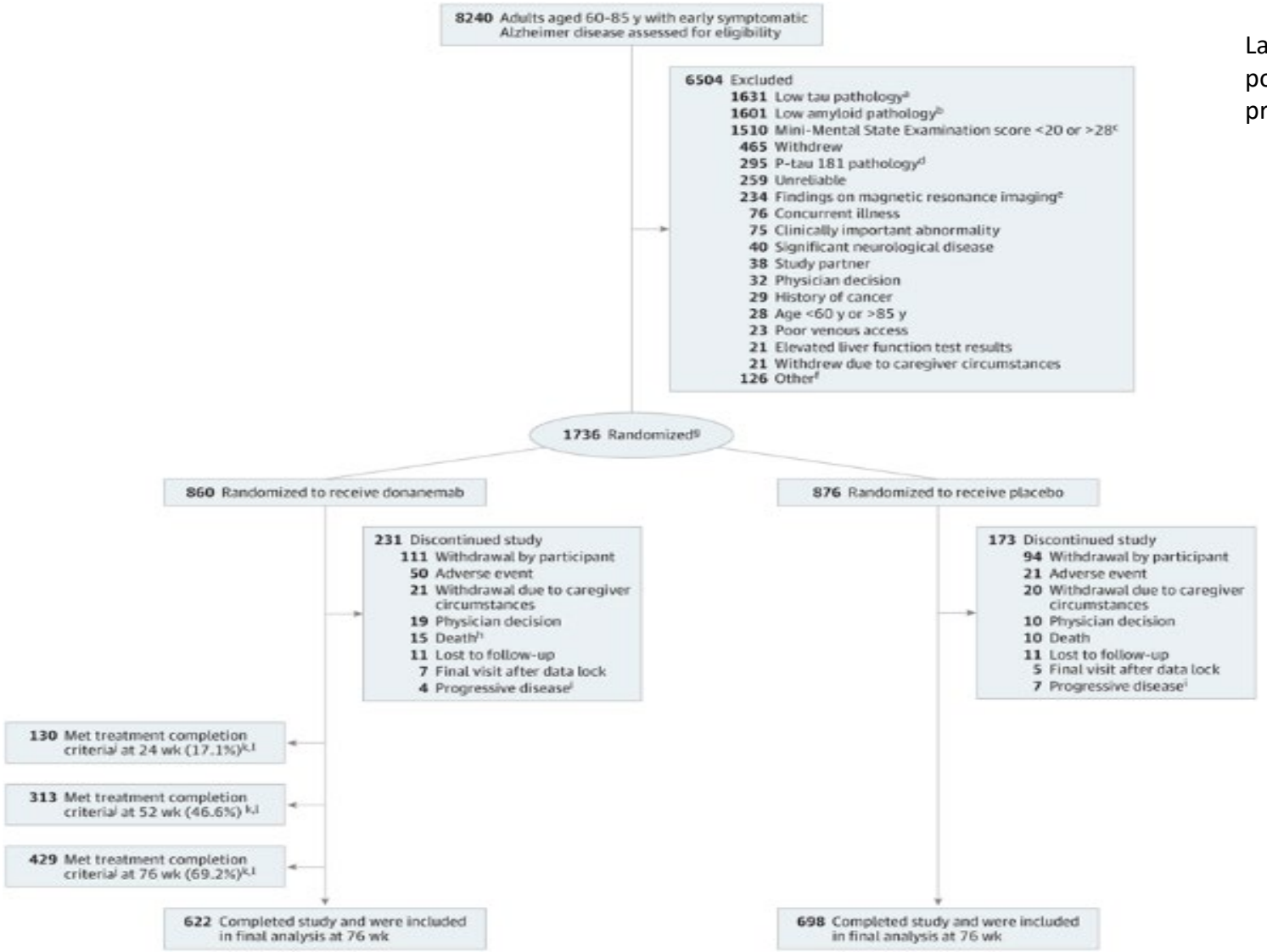
Aducanumab and lecanemab are associated with brain edema and sometimes fatal brain hemorrhages (3 patients taking lecanemab in the open-label extension of the trial died of brain hemorrhages). The brain atrophies even with normal aging, and with dementia, even more so. A 2023 review and meta-analysis of 31 randomized clinical trials of drugs that target amyloid-β reported that the drugs appeared to accelerate ventricular enlargement and brain atrophy so that patients with mild cognitive impairment who were treated with anti–amyloid-β drugs were projected to have a material regression toward the brain volumes typical of Alzheimer dementia about 8 months earlier than if they were untreated. Over 18 months, those taking the dose of lecanemab approved by the FDA had an average of 28% greater loss of brain volume than those taking placebo.

Are New Alzheimer Drugs Better than Older Drugs, JAMA Int Med, September 2023

GOALS OF STUDY

- Test efficacy of donanemab, an antibody designed to clear brain amyloid plaque in patients with mild Alzheimer disease (including MCI). Given as an intravenous infusion.
- PET scan used to select AD patients with amyloid and low/medium or high tau pathology. Age between 60-85 (rationale for cut off not explained).
- Primary outcome: integrated Alzheimer Disease Rating Scale (iADRS), a tool not routinely used by clinicians
- Numerous other outcomes reviewed, lacked statistical precision

GENERALIZABILITY WHEN ~80% EXCLUDED



Lack of diversity in the population, although better than previous studies

The Integrated Alzheimer's Disease Rating Scale (iADRS)

J Prev Alzheimers Dis. 2015 Dec 1; 2(4): 227–241.

A Combined Measure of Cognition and Function for Clinical Trials: The Integrated Alzheimer's Disease Rating Scale (iADRS)

A.M. Wessels,[1] E.R. Siemers,[1] P. Yu,[1] S.W. Andersen,[1] K.C. Holdridge,[1] J.R. Sims,[1] K. Sundell,[1] Y. Stern,[2] D.M. Rentz,[3] B. Dubois,[4] R.W. Jones,[5] J. Cummings,[6] and P.S. Aisen[7]

Scale is from 0-146, higher is better

Characteristics of clinical scales and research scales can be different

RESULTS OF iADRS

1. Over 80% of patients had clearing of amyloid (it is an anti-amyloid drug!)
2. In patients with PET scans showing low/medium tau pathology there was a significant slowing of decline
   - Treatment group declined by 6.02 points
   - Placebo group declined by 9.27
   - Difference is 3.25 points in a 146 point scale
3. In the total group (includes low/medium and high tau pathology) the difference was also about 3 points but the difference was driven by the low/medium tau pathology group
4. This translates to about a 4 month slower progression over 76 month trial
5. There was a suggestion that Black and Hispanic participants were harmed by the active intervention

PICTURE SUMMARY

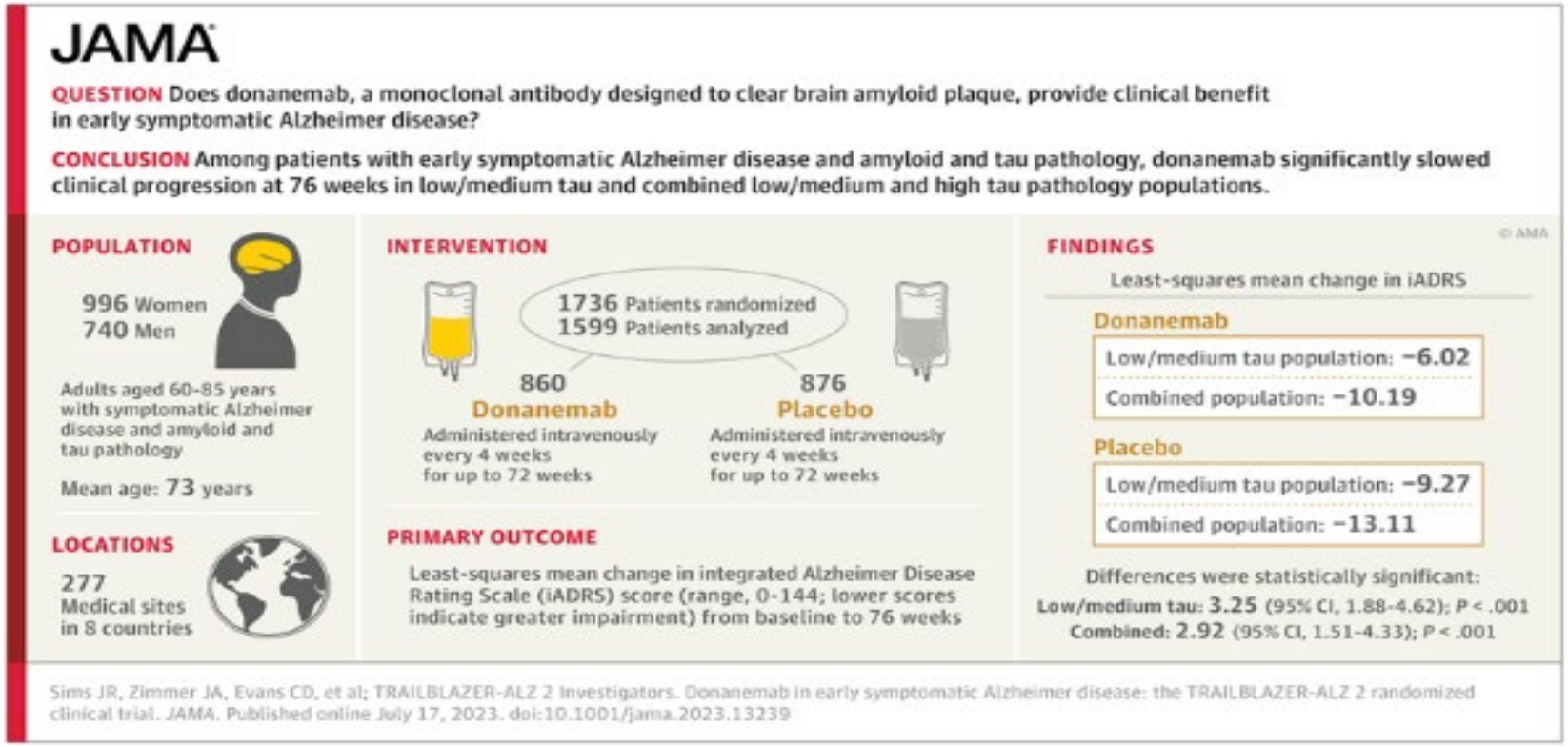


Table 3. Summary of Adverse Events (AEs) by Treatment Group

Event	Donanemab (n = 853)[a]	Placebo (n = 874)[a]
Overview of AEs, No. (%)		
Death[b]	16 (1.9)[c]	10 (1.1)
Death considered related to treatment[d]	3 (0.4)	1 (0.1)
Participants with ≥1 serious AE[e]	148 (17.4)	138 (15.8)
Treatment discontinuations due to AEs	112 (13.1)	38 (4.3)
Study discontinuations due to AEs	69 (8.1)	32 (3.7)
Participants with ≥1 treatment-emergent AE[f]	759 (89.0)	718 (82.2)
Treatment-emergent AEs ≥5% incidence, No. (%)		
ARIA-E	205 (24.0)	17 (1.9)
ARIA-H	168 (19.7)	65 (7.4)
COVID-19	136 (15.9)	154 (17.6)
Headache	119 (14.0)	86 (9.8)
Fall	114 (13.4)	110 (12.6)
Infusion-related reaction	74 (8.7)	4 (0.5)
Superficial siderosis of central nervous system	58 (6.8)	10 (1.1)
Dizziness	53 (6.2)	48 (5.5)
Arthralgia	49 (5.7)	42 (4.8)
Urinary tract infection	45 (5.3)	59 (6.8)
Diarrhea	43 (5.0)	50 (5.7)
Fatigue	42 (4.9)	45 (5.1)
Overview of ARIA[g]		
Microhemorrhage or superficial siderosis present at baseline, No. (%)	124 (14.5)	161 (18.4)
ARIA-E by *APOE* ε4 allele status, No./total No. (%)		
Noncarrier	40/255 (15.7)	2/250 (0.8)
Heterozygous carrier	103/452 (22.8)	9/474 (1.9)
Homozygous carrier	58/143 (40.6)	5/146 (3.4)
Any ARIA, No. (%)[h]	314 (36.8)	130 (14.9)
ARIA-E, No. (%)	205 (24.0)	18 (2.1)
Asymptomatic	153 (17.9)	17 (1.9)
Symptomatic	52 (6.1)	1 (0.1)[i]
ARIA-H, No. (%)	268 (31.4)	119 (13.6)
Microhemorrhage	229 (26.8)	109 (12.5)
Superficial siderosis	134 (15.7)	26 (3.0)
Intracerebral hemorrhage >1 cm	3 (0.4)	2 (0.2)

Abbreviations: *APOE*, apolipoprotein E; ARIA-E, amyloid-related imaging abnormalities of edema/effusions; ARIA-H, amyloid-related imaging abnormality of microhemorrhages and hemosiderin deposits; MRI, magnetic resonance imaging.

[a] Participants may have been counted in more than 1 category; adverse events population is defined as all participants that received at least 1 infusion.

[b] Deaths are also included under serious AEs and discontinuations due to AEs.

[c] Includes 1 death that occurred after treatment completion and in the follow-up period.

[d] Deaths related to donanemab occurred subsequent to ARIA and the death related to placebo occurred due to arteriosclerosis.

[e] Definition of serious AE: results in death, is life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability/incapacity, or based on other medical/scientific judgment.

[f] Definition of treatment-emergent adverse event: an untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.

[g] Based on safety MRI or treatment-emergent AE cluster (after baseline); *APOE4* is a known risk factor for ARIA-E.[30]

[h] Based on MRI.

[i] One placebo-treated participant had ARIA-E during the placebo-controlled period; however, the participant developed symptoms during the long-term extension period.

ADVERSE EVENTS

As well as standard list, I have other concerns

- For younger AD patients what will the damage seen on MRI mean in 10 years time? Extended follow up of the younger patients would be helpful.
- How will we organize infusion therapy? Will we require dementia treatment centres for infusions, analogous to current cancer centres?
- The support structures required: PET scans, MRIs, infusion costs, will be large even without the cost of the drug (the approved drug lecanemab is $26,000 US/year)
- Would money spent on ‘caring’ supports (home care, day programs, home-based primary care, etc.) provide better ‘bang for the buck’?

Bottom Line

Donanemab is not yet ready for clinical use, and likely will never make a huge impact

Compared to other amyloid clearing medications, it is a step forward

It might presage the development of more clinically relevant medications. There is reason for optimism.

Cost of the drug and the infrastructure required are important considerations

Thank You!

Carolyn Tan, Natasha Lane, Barry Goldlist

Questions?