Geriatrics Literature Update

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Learning objectives

- identify areas in clinical medicine where new strong evidence has been uncovered that may affect geriatric practice
- describe the results of a critical appraisal of this evidence including limitations and pitfalls of published articles;
- discuss clinical advances in caring for older adults from a review of recent select peer-reviewed journal articles.

Disclosures

- No relevant financial relationships.

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FDA NEWS RELEASE

FDA Grants Accelerated Approval for Alzheimer's Drug

For Immediate Release:

June 07, 2021

Today, the U.S. Food and Drug Administration approved Aduhelm (aducanumab) for the treatment of Alzheimer's, a debilitating disease affecting 6.2 million Americans. Aduhelm was approved using the accelerated approval pathway (/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval), which can be used for a drug for a serious or life-threatening illness that provides a meaningful therapeutic advantage over existing treatments. Accelerated approval can be based on the drug's effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients, with a required post-approval trial to verify that the drug provides the expected clinical benefit.

https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug

Aducanumab is an immunotherapeutic classified as a human immunoglobulin gamma 1 (**IgG1**) **monoclonal antibody**.

It exerts its mechanism of action by crossing the blood-brain barrier and **selectively targeting and binding** aggregated soluble oligomers and insoluble fibrils **conformations of amyloid β plaques in the brain**.

https://www.ncbi.nlm.nih.gov/books/NBK573062/

Failure to demonstrate efficacy of aducanumab: An analysis of the EMERGE and ENGAGE trials as reported by Biogen, December 2019

Alzheimer's Dement. 2021;17:696–701.

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Abstract

Aducanumab recently underwent two large phase III clinical trials that were stopped prematurely by the sponsor Biogen. One trial was trending positive while the other showed no benefits from aducanumab. Post hoc analyses led the sponsor to assert that there was a sufficient efficacy signal to justify a new drug application as a treatment for Alzheimer's disease. The sponsor claimed that subsets of participants receiving sufficiently high doses of aducanumab demonstrated benefits in both trials. In contrast, we identified alternative accounts for the apparent drug benefits in post hoc subgroups that are unrelated to dose effects. Biomarker data were consistent with target engage-

BACKGROUND: EMERGE and ENGAGE trials

In March 2019, the drug company issued a press release in which they announced that they were **halting both ADU trials for futility.**
Rationale: the prespecified outcome required that both trials had to demonstrate benefits

However, in October 2019, the drug company issued another press release in which they reported that subsequent analyses of the ADU dataset gave a different view.

In the dataset from March 20, 2019, **high-dose ADU in the EMERGE study showed benefits** in the primary outcome (CDR-SB) and in each of the other secondary outcomes (Mini-Mental State Examination [MMSE], Alzheimer's Disease Assessment Scale—Cognitive—13-item scale [ADAS-Cog-13], and Alzheimer's Disease Cooperative Study–Activities of Daily Living–for Mild Cognitive Impairment [ADCS-ADL-MCI]), while **low-dose ADU did not show benefits** compared to placebo.

No benefits were seen for low-dose or high dose ADU in the ENGAGE study.

In both the EMERGE and ENGAGE trials, amyloid PET imaging showed dose-related reductions in brain amyloid β, indicating target engagement.

That one study met its endpoints and another didn’t was considered a failure by the drug company in March 2019.

The difference in high-dose ADU exposure was the critical variable that justified the drug company’s efficacy claims based on EMERGE and the failure to see efficacy in the ENGAGE trial.

Less progression occurred in the placebo group of ENGAGE compared to EMERGE (and greater proportion in ENGAGE completed full 78 weeks)

	Intention to treat population			Subset with consent prior to week 16 in intent to treat population who received 14 treatment sessions		
	Placebo decline N = 548	Low-dose ADU N = 543	High-dose ADU N = 547	Placebo decline N = 304	Low-dose ADU N = 295	High-dose ADU N = 288
		Difference vs placebo 95% CI(%)	Difference vs placebo 95% CI(%)		Difference vs placebo 95% CI(%)	Difference vs placebo 95% CI(%)
EMERGE CDR-SB	1.74	**–0.25**	**–0.40**	1.76	**–0.42**	**–0.53**
		–0.55, 0.06(–14%)	–0.71, –0.10(–23%)		–0.94, 0.10(–24%)	–1.05, –0.02(–30%)
Percent completing Week 78	52.6%	53.2%	54.7%	24.4%	25.7%	27.8%
ENGAGE CDR-SB	1.55	**–0.18**	**0.03**	1.79	**–0.35**	**–0.45**
		–0.47, 0.12(–12%)	–0.26, 0.33(2%)		–0.88, 0.18(–20%)	–1.02, 0.06(–27%)
Percent completing Week 78	60.9%	60.9%	52.9%	26.7%	31.4%	24.5%

The larger decline in the placebo group in EMERGE is an alternative explanation for statistically significant benefits for high-dose ADU in that trial.

Alzheimer's Dement. 2021;17:702–703.

Open Peer Commentary to "Failure to demonstrate efficacy of aducanumab: An analysis of the EMERGE and ENGAGE Trials as reported by Biogen December 2019"

Marwan Noel Sabbagh MD[1] | Jeffrey Cummings MD, ScD[1,2]

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By full disclosure, MNS advises Biogen's aducanumab, Eisai's BAN2401

When human immunodeficiency virus (HIV) infection was first identified there was no approved treatment…

Similarly, lovastatin was the first β-Hydroxy β-methylglutaryl-CoA (HMG CoA) reductase inhibitor approved; …

In AD therapeutics, tacrine was the first approved treatment …

Approval of aducanumab would represent the beginning of the modern treatment era for AD similarly stimulating the field as was seen with statins and HIV treatments. This is not a cure but the first incremental step in transforming the disease from an untreatable terminal illness to a manageable chronic disease.

Annals of Internal Medicine

IDEAS AND OPINIONS

The Problem of Aducanumab for the Treatment of Alzheimer Disease

Ann Intern Med. 2021;174:1303–1304.

G. Caleb Alexander, MD, MS, and Jason Karlawish, MD

On 7 June 2021, the U.S. Food and Drug Administration (FDA) approved aducanumab for the treatment of Alzheimer disease. Biogen, the owner of the drug, will sell it as Aduhelm. The FDA's decision to approve aducanumab is among its most controversial ever. In this article, we examine the decision's implications for clinical research and patient care.

Reverberating Problems With Drug Approval and Research

Aducanumab was approved despite the concerns of scientists and regulatory experts about its efficacy. Notably, an FDA statistician and an advisory committee on which one of us served (G.C.A.) reviewed the product at a November 2020 hearing and concluded that it

Aducanumab's approval will have notable impacts on drug development and regulation. The FDA's willingness to accept amyloid as a surrogate may prompt Biogen and other companies to seek approval for other drugs that reduce levels of amyloid or other biomarkers but have unclear clinical benefits. Persons living with Alzheimer disease may choose to drop out of or not enroll in clinical trials and instead take Aduhelm. This decision is of course their ethical privilege, and if aducanumab were effective, their collective action could revolutionize Alzheimer disease trials (8). Imagine, for example, head-to-head comparison studies to show which of 2 treatments is safer and more effective.

We can only imagine—aducanumab's clinical benefits have not been validated. In reality, as desperate patients understandably take it and possibly other amyloid-reduc-

FDA approved Aducanumab, using an "accelerated approval" pathway that the advisory committee had been informed was not being considered.

Under accelerated approval, **a drug is approved on the basis of its effect on a surrogate marker of a disease**—in this instance, brain β -amyloid levels—rather than clinical outcomes, such as signs or symptoms of Alzheimer disease.

As the drug manufacturer sells Aducanumab, it is **required to conduct a randomized controlled clinical trial to confirm its clinical benefits; the company has stated that the study will be completed by 2030**.

Accelerated approval is intended for products expected to provide a meaningful advantage over available therapies for a serious disease but for which there is uncertainty about clinical benefit.

How do these conditions align with aducanumab?

- serious disease
- no proven therapies
- elevated measures of β –amyloid, & τ protein, are diagnostic pathology
- Aducanumab's phase 1 study indicates the drug reduces β -amyloid levels

Whether β –amyloid alone is a valid surrogate for treatment of Alzheimer disease is unclear. Now, treatment of an amyloid level is suddenly clinical practice.

BMJ 2021;374:n1682

Aducanumab for Alzheimer's disease?

Patients and families need hope, not false hope

Sebastian Walsh, [1] Richard Merrick, [1] Richard Milne, [2] Carol Brayne[1]

The US licensing of Biogen's aducanumab as "the first ever disease modifying drug for Alzheimer's disease" was hailed as a major advance by many. However, in response to the decision, three members of the Food and Drug Administration's expert independent advisory committee, which voted almost unanimously against approval, resigned, with Harvard professor of medicine Aaron Kesselheim

abundant evidence of no benefit,[5 6] including the negative, identically designed trial.

Years of uncertainty

Attempting reassurance, the FDA committed Biogen to a nine year post-approval confirmatory study. So we may not know until at least 2030 whether aducanumab slows cognitive decline, during which

The FDA committed the drug company to a nine year post-approval confirmatory study. So **we may not know until at least 2030 whether aducanumab slows cognitive decline**, during which time the drug will be sold for use at a cost of $56 000 per person each year. ***[In January 2022, Biogen reduced the average annual cost to $28,200.]***

Moreover, **phase IV post-approval trials may not be able to establish efficacy or lack thereof since, unlike pre-approval trials, they are designed primarily to identify rare side effects and real world effectiveness.**

What will happen outside the US?

The dementia drugs **donepezil, galantamine, rivastigmine, and memantine were defunded in France in 2018** after over a decade of use because there was no evidence of clinically meaningful benefit.

In 2018, the **European Medicines Agency** (including the UK) **updated its guidelines on clinical trials** for Alzheimer's disease to **emphasize the need for trials to show cognitive and functional benefits** rather than focusing solely on surrogate endpoints such as amyloid plaques.

Approval of aducanumab in Europe would be inconsistent with this guidance and is therefore unlikely.

Even if approved, bodies such as the UK National Institute for Health and Care Excellence would **struggle to reconcile uncertain clinical efficacy with the cost of treatment**: as well as monthly intravenous infusions for an indefinite period, **patients require repeated magnetic resonance imaging to monitor for side effects**; 35% of patients in the trials experienced brain edema and 19% micro-hemorrhages at the recommended dose.

U.S. approval of aducanumab has consequences for trials of other potential Alzheimer's treatments.

- decide whether to use aducanumab or placebo as a control intervention
- use of placebo controls will be challenging when there is an FDA approved drug

Potential consequences:

- damage of public trust in regulatory and licensing institutions
- sensitive situation, especially during a pandemic (when trying to improve vaccination rate)

Aducanumab's approval on a technicality could undermine regulatory standards designed to protect against false hope and "set a dangerous precedent."

Some see aducanumab as proof of concept for the amyloid cascade theory, justifying decades of unsuccessful research costing billions of pounds and exposing thousands of participants to the side effects of experimental treatments. **Others fear it will simply encourage futile investment** in anti-amyloid therapies, diverting funds away from effective prevention measures such as improving physical activity or reducing hypertension, and better support after diagnosis.

JAMA May 4, 2021 Volume 325, Number 17 1717-1718.

VIEWPOINT

Evaluation of Aducanumab for Alzheimer Disease
Scientific Evidence and Regulatory Review Involving Efficacy, Safety, and Futility

G. Caleb Alexander, MD, MS
Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; and Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland.

On November 6, 2020, a US Food and Drug Administration (FDA) advisory committee reviewed issues related to the efficacy and safety of aducanumab, a human IgG1 anti-Aβ monoclonal antibody specific for β-amyloid oligomers and fibrils implicated in the pathogenesis of Alzheimer disease.[1] Given the importance of drug innovation for this common and often devastating disease, the abandonment of prior monoclonal antibodies targeting β-amyloid, and the clinical, regulatory, and market effects that approval of aducanumab could have, there has been significant interest in the development and regulacteristics that "support the persuasiveness of a single trial in supporting the conclusion that there is substantial evidence of effectiveness."[4] In the case of aducanumab, the sponsor worked with the FDA to further analyze the pivotal trials as well as its earlier phase 1b study to determine the importance of the statistically significant results of the high-dose group compared with the placebo group in study 302. This undertaking reflected an unusual degree of collaboration between the FDA and manufacturer of aducanumab, and the arrangement has been criticized as having potentially compromised the FDA's objectivity in reviewing the

Clinical Dementia Rating global score

RATING

CDR-0: no cognitive impairment

CDR-0.5: questionable or very mild dementia

CDR-1: mild

CDR-2: moderate

CDR-3: severe

.

Score is calculated via an algorithm

CDR™ Scoring Table

Subject Initials ___

CLINICAL DEMENTIA RATING (CDR™):	0	0.5	1	2	3

	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

https://naccdata.org/data-collection/tools-calculators/cdr

Morris, J.C. (1993). The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology, 43, 2412–2414.

Clinical Dementia Rating scale – Sum of Boxes (CDR-SB)

Table 5. Dementia Severity Categories Based on CDR-SB Scores

CDR-SB Range	Staging Category
0	Normal
0.5-4.0	Questionable cognitive impairment
0.5-2.0	Questionable impairment
2.5-4.0	Very mild dementia
4.5-9.0	Mild dementia
9.5-15.5	Moderate dementia
16.0-18.0	Severe dementia

Abbreviation: CDR-SB, Clinical Dementia Rating Scale Sum of Boxes score.

In addition, **the minimum clinically important difference of the primary end point used in the aducanumab trials, CDR-SB, is generally considered to be 1 to 2 on a scale from 0 to 18**, while the 22% **reduction in the CDR-SB outcome observed in the high-dose group in study 302 (EMERGE) reflected an absolute difference of 0.39**. The FDA endorsed any statistically significant effect on the CDR-SB as a clinically meaningful outcome in studies 301 (ENGAGE) and 302 (EMERGE), but a "responder analysis," while prespecified, was not presented to the advisory committee to allow for an understanding of the proportion of individuals who achieved a predefined level of improvement at a given point.

CDR = Clinical Dementia Rating scale – Sum of Boxes

COMMENTARY

Journal of the
American Geriatrics Society

My head just exploded, now what? Aducanumab

J Am Geriatr Soc. 2021, Sep;69(9):2689-2691.

Nancy E. Lundebjerg MPA

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Have you ever pushed a person in a wheelchair while in search of a diagnosis which would then (hopefully) lead to a cure?

drug with the requirement that Biogen conduct an additional trial.[4–6]

It is important to note that although aducanumab

FDA approval terminology: AD vs mild *

Tone down rhetoric from trusted organizations

Provide context

Adequate FDA follow-up

It is important to note that although aducanumab was studied only in patients with mild cognitive impairment or early-stage Alzheimer's disease, FDA has approved it for the treatment of Alzheimer's disease writ large. Looking ahead to direct-to-consumer marketing, the FDA-approved label[7] will be marketed as saying "if you have Alzheimer's disease, this drug is for you." You probably would not guess that from the Biogen CEO statement which characterized the company's new blockbuster drug as having the potential to help change the way patients are diagnosed and treated while noting that pricing reflects value to the patient, caregivers, and families while also enabling continuous innovation.[8]

This is the part where my head explodes.

*Drug label changed from 06/21 (AD) to 07/21 (MCI/ mild dementia) **

J Am Geriatr Soc. 2021, Sep;69(9):2689-2691.

Aduhelm
aducanumab

UnitedHealthcare Nursing Home Plan SNP: N: Not Covered

Entire Monograph

Adult Dosing

Dosage forms: INJ

Special Note

[formulation clarification]

Info: nonproprietary name = aducanumab-avwa

Alzheimer dz, mild cognitive impairment or mild dementia

[10 mg/kg/dose IV q4wk]

Start: 1 mg/kg/dose IV q4wk x2 doses, then 3 mg/kg/dose IV q4wk x2 doses, then 6 mg/kg/dose IV q4wk x2 doses, then 10 mg/kg/dose IV q4wk; Info: confirm presence of amyloid beta pathology before tx initiation; use ABW to calculate dose; give doses >21 days apart; see pkg insert for dose interruption recommendations based on MRI and symptom severity

renal dosing

[not defined]

renal impairment: not defined

HD/PD: not defined

hepatic dosing

[not defined]

Contraindications / Cautions

- hypersens. to drug/class/compon.
- caution: cerebral microhemorrhage
- caution: superficial siderosis

Drug Interactions

Overview

aducanumab

Interaction Characteristics:
None

No significant interactions known or found for this drug. Caution always advised with multiple medications.

Adverse Reactions

Serious Reactions

- hypersensitivity rxn
- cerebral edema, amyloid-related
- cerebral microhemorrhage, amyloid-related
- superficial siderosis, amyloid-related
- seizures

Common Reactions

- amyloid-related imaging abnormalities
- headache
- diarrhea
- altered mental status

Safety/Monitoring

Monitoring Parameters
MRI w/in 1y prior to tx start, then prior to 5th infusion (1st dose of 6 mg/kg), 7th infusion (1st dose of 10 mg/kg), 9th infusion (3rd dose of 10 mg/kg), and 12th infusion (6th dose of 10 mg/kg), then as clinically indicated

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Special Article

J Prev Alz Dis 2021;4(8):398-410.

Aducanumab: Appropriate Use Recommendations

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Abstract

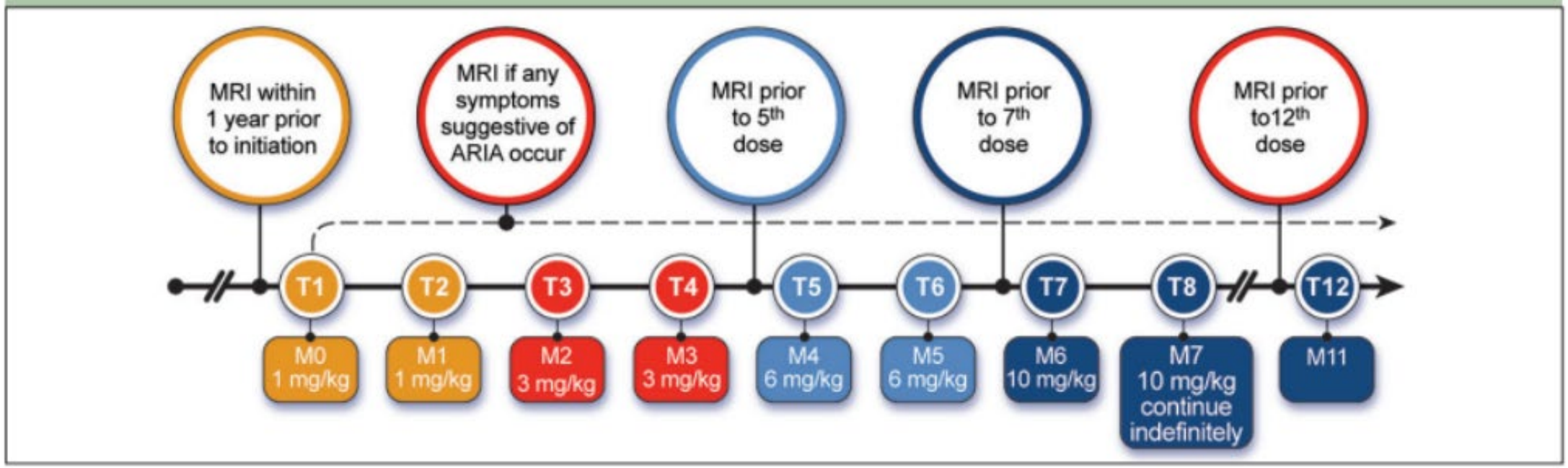
Aducanumab has been approved by the US Food and Drug Administration for treatment of Alzheimer's disease (AD). Clinicians require guidance on the appropriate use of this new therapy. An Expert Panel was assembled to construct Appropriate Use Recommendations based on the participant populations, conduct of the pivotal trials of aducanumab, updated Prescribing Information, and expert consensus. Aducanumab is an amyloid-targeting monoclonal antibody provides key facts on aducanumab such as dose, titration, pharmacokinetics, and side effects. The Clinical Studies section describes the clinical trials that led to the approval of aducanumab. Many details of the clinical use of this new agent are not detailed in the Prescribing Information (1) and there is a need for specific recommendations regarding how to use aducanumab appropriately. Experts with experience in AD research, AD clinical

Exclusion Criteria

Table 1. Clinical trial enrollment criteria and appropriate use criteria for aducanumab in clinical practice

Participant Feature	Clinical Trial Enrollment Criteria	Appropriate Use in Clinical Practice
Age	50-85	Younger or older patients meeting all other criteria for treatment could be considered candidates for aducanumab
Diagnosis	Clinical criteria for MCI due to AD or mild AD dementia	Clinical criteria for MCI due to AD or mild AD dementia
Scale scores at baseline	CDR Global Score 0.5; MMSE 24-30; RBANS Delayed Memory Score of 85 or less	MMSE 21-30 or equivalent such as MoCA 17-30
Amyloid status	Amyloid positive PET (visual read)	Amyloid positive PET (visual read) or CSF findings consistent with AD
Genetic testing	Consent for APOE genotyping	Genotyping should be discussed with the patient/care partner. ARIA risk should be described, and the patient's preferences assessed.
Neurological examination	Non-AD neurological disorders, stroke, and TIA excluded	Non-AD neurological disorders excluded
Cardiovascular history	Angina; myocardial infarction; congestive heart failure excluded	Stable cardiovascular conditions required; clinical decision can be exercised on the ability of the patient to participate safely with the therapeutic regimen
Medical history	Excluded: clinically significant systemic illness; diabetes than cannot be managed; uncontrolled hypertension (systolic > 165; diastolic > 100); history of cancer unless in remission for 5 years or localized to skin or prostate; impaired liver function; hepatitis; HIV infection	Stable medical conditions required; clinical decision can be exercised on the ability of the patient to participate safely with the therapeutic regimen
Psychiatric history	Unstable psychiatric illness in the past 6 months; alcohol or substance abuse in the past year; use of cannabinoids; positive urine tests for excluded substances	Must be stable psychiatrically; clinical decision can be exercised on the ability of the patient to participate safely with the therapeutic regimen
Reproductive status	Female subjects who are pregnant or breast feeding excluded; female subjects who are of childbearing age must be practicing contraception	Female subjects who are pregnant or breast feeding excluded; female subjects who are of childbearing age must be practicing contraception
Clotting status	Bleeding disorders, anticoagulants excluded	Patients on anticoagulants are excluded
Concomitant medications	Cholinesterase inhibitors and memantine allowed	Patients can be on standard of care with cholinesterase inhibitors and memantine
Baseline MRI	Baseline MRI finding that excluded participation: acute or subacute hemorrhage, macrohemorrhage, greater than 4 microhemorrhages, cortical infarction (>1.5 cm), 1 lacunar infarction (>1.5 cm), superficial siderosis, or diffuse white matter disease	Patients should be excluded if there is evidence of acute or subacute hemorrhage, macrohemorrhage, greater than 4 microhemorrhages, cortical infarction (>1.5 cm), 1 lacunar infarction (>1.5 cm), > 1 area of superficial siderosis, or diffuse white matter disease
Care support	Reliable informant or care partner	May be living independently or with a care partner
Informed consent	Must be signed by participant and care partner	Patient and care partner must understand the nature and requirements of therapy (e.g, monthly infusions to be performed indefinitely) and the expected outcome of therapy (slowing of decline of clinical features)

Figure 1. Aducanumab dosing and MRI monitoring schedule (Prescribing Information (1) and Expert Panel recommendation; © J Cummings; illustrator M de la Flor, PhD)



Reported adverse effects of Aducanumab in clinical trial studies:

- ARIA-edema (ARIA-E) (35%)*
- ARIA-hemosiderin deposition (ARIA-H) microhemorrhage (19%)*
- ARIA-H superficial siderosis (15%)*
- Headache (21%)
- Fall (15%)
- Diarrhea (9%)
- Confusion/delirium/altered mental status/disorientation (8%)
- Hypersensitivity (angioedema, urticaria) (<1%)
- Immunogenicity (<1%)

***Amyloid related imaging abnormalities (ARIA)**

https://www.ncbi.nlm.nih.gov/books/NBK573062/#:~:text=Aducanumab%20is%20a%20medication%20used,the%20management%20of%20Alzheimer%20disease.

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Journal of the
American Geriatrics Society

JAGS. 2022;70(6):1685–1694.

Public opinion regarding U.S. Food and Drug Administration approval of aducanumab and potential policy responses: A nationally representative survey

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Abstract

Background: Despite controversy among experts regarding aducanumab's approval by the U.S. Food and Drug Administration, little is known about public opinion on this matter.

While approximately three-quarters of respondents were initially unfamiliar with aducanumab, respondents were **less supportive of the drug's approval** once given information about the drug's potential clinical and economic impact.

Sixty-three percent of respondents support **restricting aducanumab access to patients most likely to benefit**.

1025 respondents

Eighty-one percent agree aducanumab should be **withdrawn from the market if confirmatory trials fail**.

The median respondent was **willing to pay $1–5 in higher Part B premiums** to cover aducanumab.

API Colombian Trial of Crenezumab Missed Primary Endpoints

ARTICLE | COMMENTS | REFERENCES | FURTHER READING

18 Jun 2022

Crenezumab failed to slow cognitive decline in the Alzheimer's Prevention Initiative's Colombian study, according to topline findings released June 15. Both primary endpoints were negative, although trends on the primaries and on multiple secondary and exploratory endpoints numerically favored crenezumab. Crenezumab, made by Roche/Genentech, is unique among anti-amyloid antibodies in late-stage trials because it targets Aβ oligomers and does not budge plaque load. Researchers are now analyzing target engagement, dose exposure, subgroup effects, and biomarker data; those data will be presented on August 2 at the Alzheimer's Association International Conference in San Diego and virtually.

- Crenezumab did not slow cognitive decline in this autosomal-dominant AD

"The [results] are disappointing, but not altogether unpredicted based on earlier failures of

https://www.alzforum.org/news/research-news/api-colombian-trial-crenezumab-missed-primary-endpoints

Landmark Alzheimer's prevention trial unable to show significantly slower cognitive decline in inherited form of disease

Groundbreaking Colombian study will still have major impact on Alzheimer's prevention research

https://www.bannerhealth.com/newsroom/press-releases/alzheimers-trial-unable-to-show-significantly-slower-cognitive-decline-in-inherited-form-of-disease

JAMA. Sep 13, 2022: Vol 328, No. 10

Medical News & Perspectives

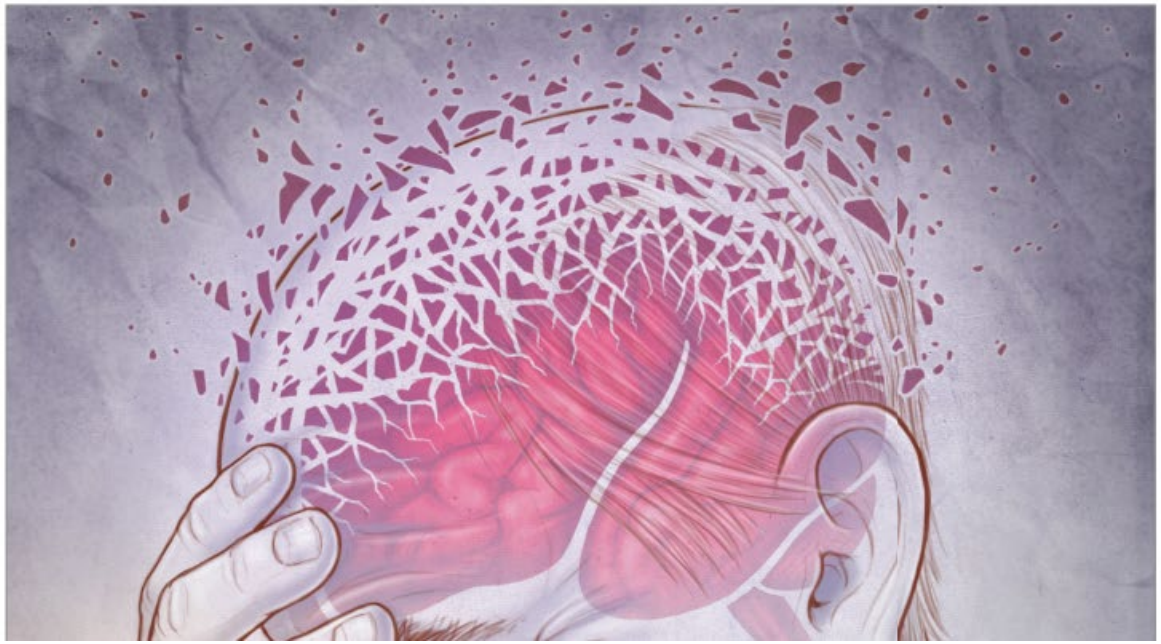
Much Anticipated Alzheimer Disease Prevention Trial Finds No Clinical Benefit From Drug Targeting Amyloid; Highlights Need to Consider Other Approaches

Rita Rubin, MA

The Paisa mutation, nicknamed for the people of northwest Colombia's Antioquia region in whom it is found, is associated with sticky clumps of protein in the brain called amyloid-β plaques, one of the hallmarks of Alzheimer disease.

Individuals who inherit a copy of the Paisa mutation—E280A in the presenilin 1 gene—from one of their parents develop mild cognitive impairment by 44 years of age, on average, and Alzheimer disease 5 years after that. Typically, they die within a few years after their 59th birthday.

+ Medical News website



Crenezumab: a humanized monoclonal immunoglobulin G4 antibody targeting β-amyloid oligomers

The trial enrolled **252 cognitively healthy people from a 6,000-person-strong registry GNA had built with the Colombian kindred,** which includes 1,200 **carriers of the E280A Paisa mutation** in presenilin 1.

Trial participants, two-thirds of whom have the mutation, received **biweekly subcutaneous injections of crenezumab or placebo for five to eight years**. Participants were not told their mutation status, and noncarriers were assigned placebo. **Dose of crenezumab was increased twice during this period.**

Crenezumab: a humanized monoclonal immunoglobulin G4 antibody targeting β-amyloid oligomers

IMAGING: florbetapir amyloid PET, FDG PET, volumetric MRI
BLOOD SAMPLES: biomarkers

The trial **did not demonstrate a significant clinical benefit in either of its co-primary endpoints** assessing the rate of change in cognitive abilities or episodic memory function, measured by the Alzheimer's Prevention Initiative (API) ADAD Composite Cognitive Test Score and the Free and Cued Selective Reminding Test (FCSRT) Cueing Index, respectively.

Research

JAMA Neurol. 2022 Sep 19: e222909. doi: 10.1001

JAMA Neurology | Original Investigation

Evaluating the Safety and Efficacy of Crenezumab vs Placebo in Adults With Early Alzheimer Disease

Two Phase 3 Randomized Placebo-Controlled Trials

Susanne Ostrowitzki, MD; Tobias Bittner, PhD; Kaycee M. Sink, MD; Howard Mackey, PhD; Christina Rabe, PhD; Lawrence S. Honig, MD, PhD; Emanuele Cassetta, MD; Michael Woodward, MD; Mercè Boada, MD; Christopher H. van Dyck, MD; Timo Grimmer, MD; Dennis J. Selkoe, MD; Andres Schneider, MD; Kathleen Blondeau, PhD; Nan Hu, PhD; Angelica Quartino, PhD; David Clayton, PhD; Michael Dolton, PhD; Yifan Dang, MS; Beth Ostaszewski, BS; Sandra M. Sanabria-Bohórquez, PhD; Michael Rabbia, MA; Balazs Toth, MS; Udo Eichenlaub, PhD; Jillian Smith, BSc; Lee A. Honigberg, PhD; Rachelle S. Doody, MD, PhD

IMPORTANCE Alzheimer disease (AD), a neurodegenerative disease characterized by β-amyloid plaques and τ tangles in the brain, represents an unmet medical need with no fully approved therapeutics to modify disease progression.

OBJECTIVE To investigate the safety and efficacy of crenezumab, a humanized monoclonal immunoglobulin G4 antibody targeting β-amyloid oligomers, in participants with prodromal to mild (early) AD.

Supplemental content

DESIGN, SETTING, AND PARTICIPANTS:
Two phase 3 multicenter randomized double-blind placebo-controlled parallel-group efficacy and safety) **global multicenter studies in persons with early AD.**

CREAD (2016, 194 sites in 30 countries)
CREAD2 (2017, 209 sites in 27 countries)

Both trials enrolled individuals aged **50 to 85 years with early AD**.

409 participants in the placebo group and 404 in the crenezumab group in CREAD
399 in the placebo group and 407 in the crenezumab group in CREAD2
Data were analyzed up until January 2019 and August 2019, respectively.

INTERVENTIONS: Participants received placebo or **60mg/kg crenezumab intravenously every 4 weeks** for up to 100 weeks.

MAIN OUTCOMES AND MEASURES: The primary outcome was change from baseline to week 105 in Clinical Dementia Rating–Sum of Boxes (CDR-SB) score.

RESULTS: The between-group difference in mean change from baseline in CDR-SB score (placebo minus crenezumab) was −0.17 (95%CI, −0.86 to 0.53; P = .63) at week 105 in the CREAD study **(88 placebo; 86 crenezumab)**.

CONCLUSIONS AND RELEVANCE: Crenezumab was well tolerated but did not reduce clinical decline in participants with early AD.

2

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PMCID: PMC3433229

NIHMSID: NIHMS396197

PMID: 22762316

Cognitive Trajectories after Postoperative Delirium

Jane S. Saczynski, Ph.D., Edward R. Marcantonio, M.D., Lien Quach, M.P.H., M.S., Tamara G. Fong, M.D., Ph.D., Alden Gross, Ph.D., M.P.H., Sharon K. Inouye, M.D., M.P.H., and Richard N. Jones, Sc.D.

JACEP Open 2020;*1:812–823.*

DOI: 10.1002/emp2.12110

WILEY

REVIEW ARTICLE

Geriatrics

The agitated older adult in the emergency department: a narrative review of common causes and management strategies

Maura Kennedy MD, MPH[1,2] | Jennifer Koehl PharmD[1,3] | Christina L. Shenvi MD, PhD[4] | Allyson Greenberg PharmD[5,6] | Olivia Zurek MD[7,8] | Michael LaMantia MD, MPH[9] | Alexander X. Lo MD, PhD[10]

COMMON CAUSES OF AGITATION IN OLDER ADULTS:

- Pre-existing psychiatric condition
- Intoxication (alcohol or other substances)
- Dementia with behavioral and psychiatric symptoms
- Delirium
  - (hallmark is reduced attention span)
  - 3 psychomotor subtypes: hypoactive, hyperactive, and mixed

MANAGEMENT OPTIONS:

- Non-pharmacologic
- Pharmacologic *(for rapid management of the agitation, such as when the patient is at imminent risk of harm to self or others)*

Pain Assessment in Advanced Dementia Scale (PAINAD)

TABLE 2 The Pain Assessment in Advanced Dementia Scale[35]: an observational pain scale for use in individuals with dementia

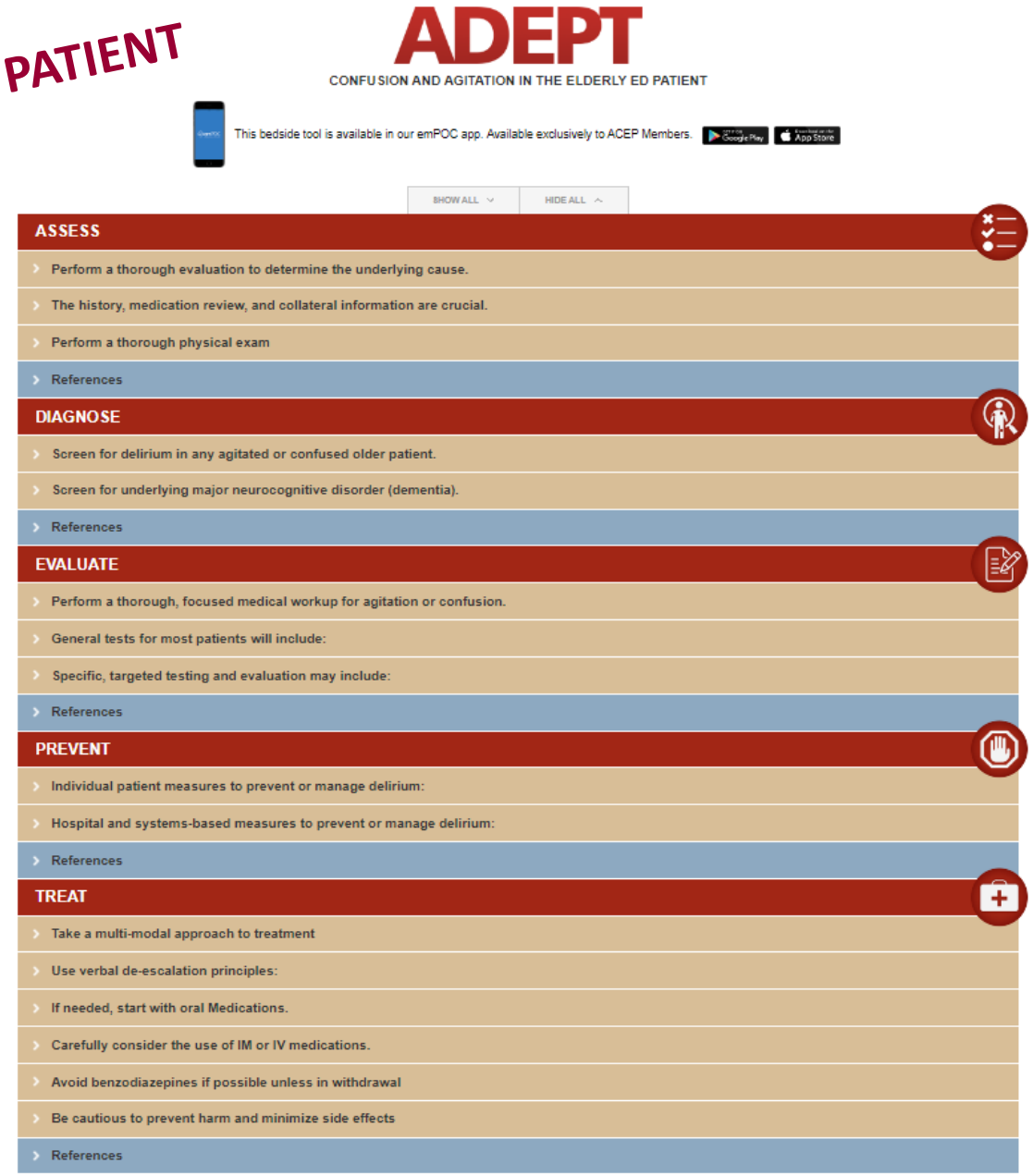
Item	Score = 0	Score = 1	Score = 2	Sum of scores
Breathing independent of vocalization	Normal	• Occasional labored breathing • Short period of hyperventilation	• Noisy labored breathing • Long period of hyperventilation • Cheyne-stokes respirations	
Negative vocalization	None	• Occasional moan or groan • Low-level of speech with a negative or disapproving quality	• Repeated troubled calling out • Loud moaning or groaning • Crying	
Facial expression	Smiling or inexpressive	• Sad • Frightened • Frown	• Facial grimacing	
Body language	Relaxed	• Tense • Distressed pacing • Fidgeting	• Rigid • Fists clenched • Knees pulled up • Pulling or pushing away • Striking out	
Consolability	No need to console	• Distracted or reassured by voice or touch	• Unable to console, distract or reassure	
				Total score range: 0–10

Mild pain: score 1–3; moderate pain: score 4–6; severe pain: score 7–10

CONFUSION AND AGITATION IN THE ELDERLY ED PATIENT

- **A**SSESS
- **D**IAGNOSE
- **E**VALUATE
- **P**REVENT
- **T**REAT

https://www.acep.org/patient-care/adept/



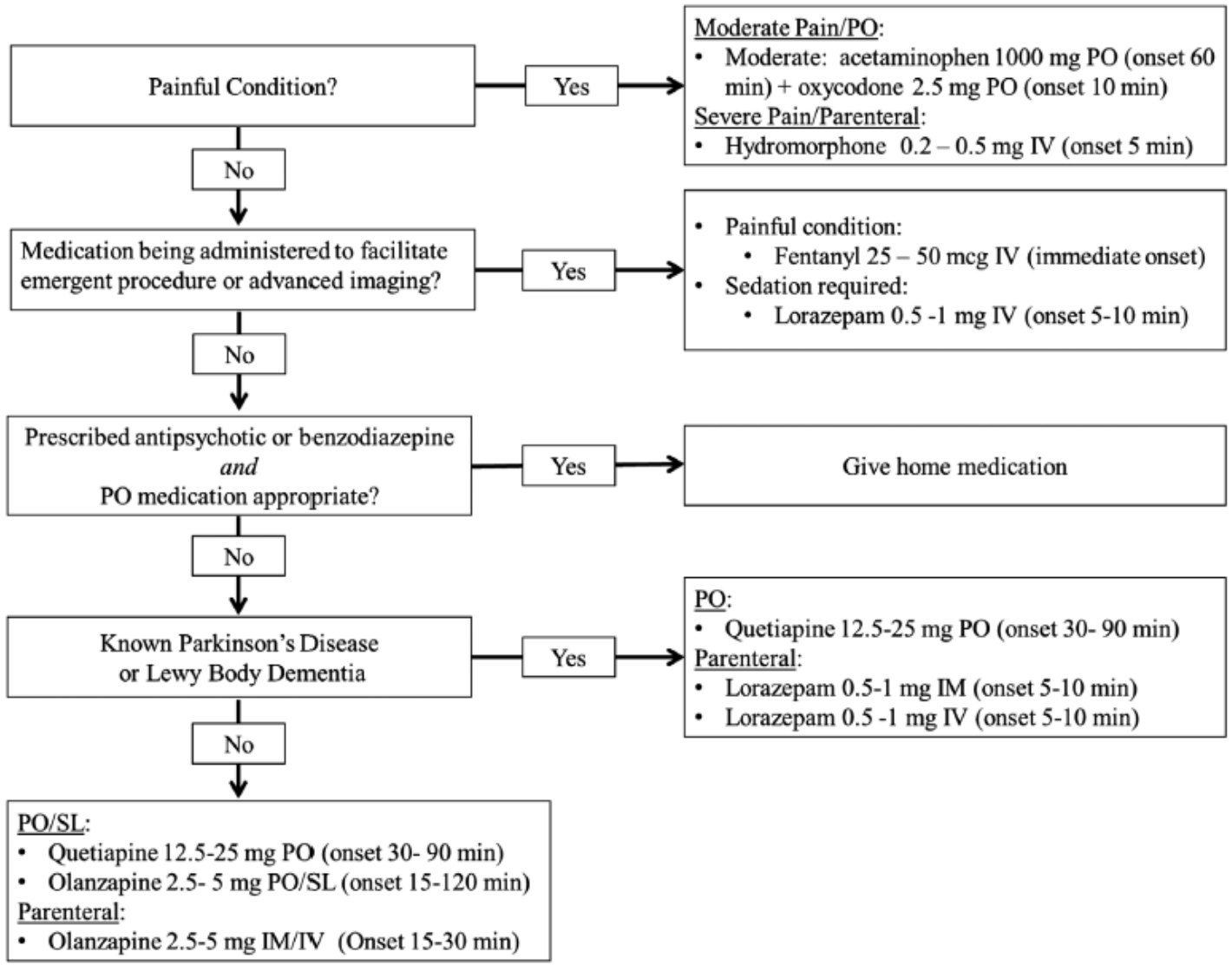


FIGURE 1 Potential framework to guide selection of pharmacologic agent to manage agitation in older emergency department patients. IM, intramuscular; IV, intravenous; PO, per os/by mouth; SL, sublingual

3

Latour *et al. BMC Geriatrics* (2022) 22:187
https://doi.org/10.1186/s12877-022-02866-2

BMC Geriatrics

RESEARCH Open Access

Nursing home residents with suspected urinary tract infections: a diagnostic accuracy study

Katrien Latour[1,2*], Jan De Lepeleire[2], Boudewijn Catry[1,3] and Frank Buntinx[2,4]

Abstract

Background: Urinary tract infections (UTIs) are one of the most common infections in nursing homes (NHs). A high error rate of a UTI diagnosis based solely on clinical criteria is to be expected in older persons as they often present infections in an atypical way. A study was set up to assess the diagnostic value of signs/symptoms and urine dipstick testing in identifying UTIs in NH residents and to explore whether C-reactive protein (CRP) measured by point-of-care testing (POCT) can help in the diagnosis.

Methods: During a three month prospective multicentre study, urine sampling for culture, POCT CRP and urinary dipstick testing were performed in each NH resident with a suspected UTI. UTIs were defined according to Stone et al., i.e. criteria based upon the presence of a set of signs/symptoms and a positive urine culture.

METHODS:

- **Three month prospective multicenter study**;
- **urine culture, POCT CRP and urinary dipstick testing** were performed in each NH resident with a suspected UTI;
- UTIs were defined according to Stone et al criteria (set of signs/symptoms + positive urine culture

RESULTS:

- Eleven NHs and 1263 residents participated.
- **Sixteen out of 137 recorded UTI suspicions were confirmed.**
- **Acute dysuria and acute suprapubic pain were found to be significant predictors.**
- **The combined nitrite and leucocyte esterase urine dipstick test (one or both positive) had a high negative predictive value. (i.e. greater sensitivity)**

CONCLUSIONS:

- **Using a stringent definition, only 11.7% of our suspicions were confirmed.**

- Besides acute dysuria and suprapubic pain, not able to prove that any other clinical sign/symptom or POCT CPR adds useful information to the UTI diagnosis.

- **Confirmed the findings of earlier research** that **urine dipstick tests are useful in ruling out UTIs and identified a potential overuse of antimicrobials in their NH population**.

DOI: 10.1111/jgs.17638

CLINICAL INVESTIGATIONS

Journal of the
American Geriatrics Society

JAGS 2022;70:1070–1081.

Overdiagnosis of urinary tract infections by nursing home clinicians versus a clinical guideline

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Abstract

Purpose: To inform overprescribing and antibiotic stewardship in nursing homes (NHs), we examined the concordance between clinicians' (NH primary

METHODS:

- **cross-sectional web-based survey** of a U.S. national convenience sample of NH clinicians
- **19 randomly selected clinical scenarios** of NH residents with possible UTIs
- for each scenario, participants were asked if they thought a UTI was likely

RESULTS:

- 1748 NH clinicians responded to 33,212 discrete choice scenarios;
- 867 **(50%) were NH primary care providers**
- 881 **(50%) were NH registered nurses**
- 39% were male, mean age was 45 years
- Uncertain about diagnosis in 30% of scenarios

RESULTS:

- **Correct classification for 66% of all scenarios** (providers: 70%; nurses: 62%)
- Compared to the clinical guideline,
- **Respondent judgment had a sensitivity of 78%** (providers: 81%; nurses: 74%)
  [higher sensitivity = fewer false negatives]
  and specificity of 54% (providers: 59%; nurses: 49%)
  [lower specificity = overdiagnosis]
  [higher specificity = fewer false positive results]
- Being a nurse and having higher closemindedness were associated with higher odds of false positive UTI
- Higher UTI knowledge and conscientiousness were associated with lower odds of false positive UTI ratings

CONCLUSIONS:

Clinicians tend to over-diagnose urinary tract infections, necessitating systems-based interventions to augment clinical decision-making.

Guideline based decision tree of urinary tract infection diagnosis in nursing homes

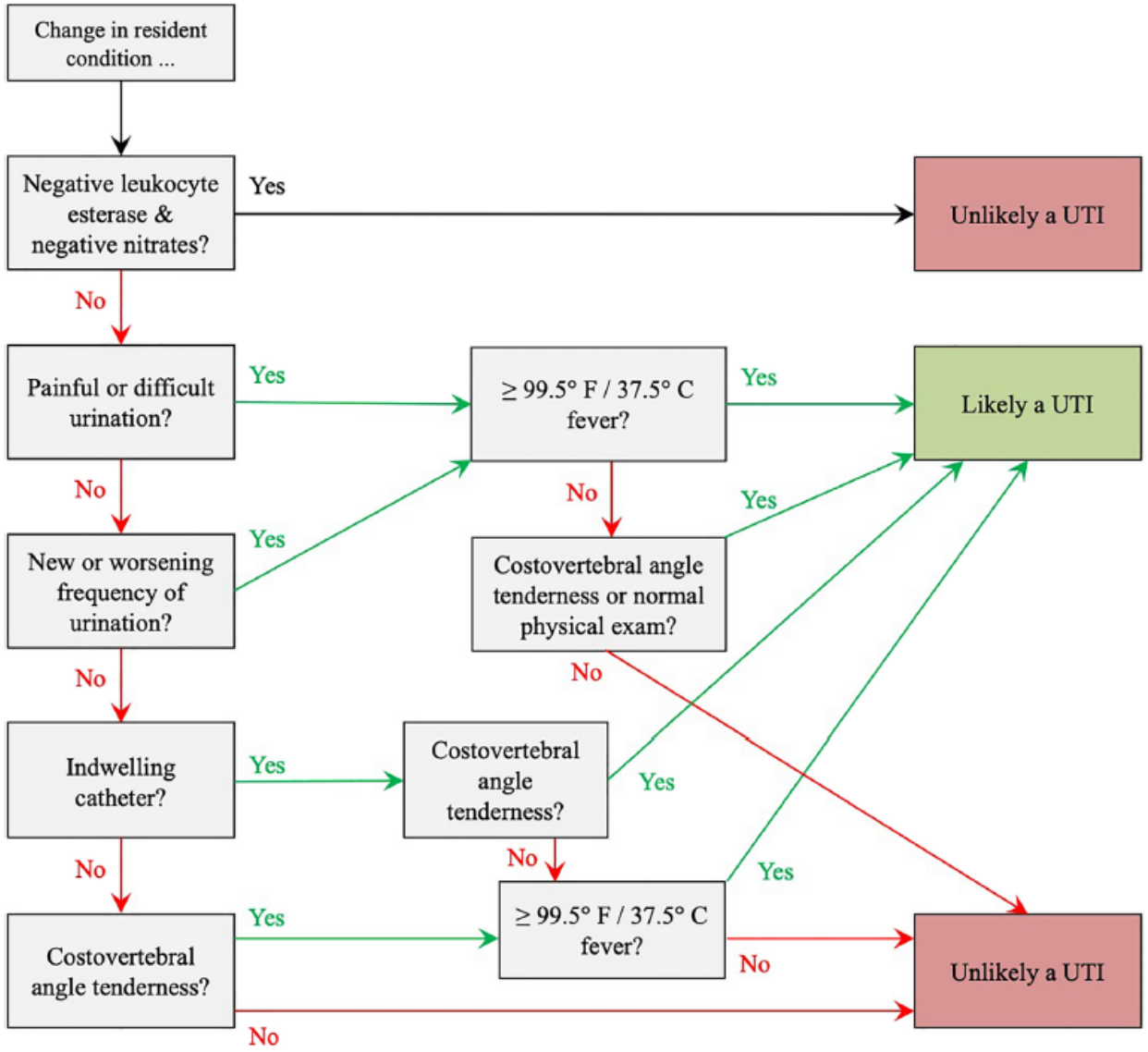

FIGURE 1 Guideline-based decision tree of urinary tract infection diagnosis in nursing homes

Published in final edited form as:
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Diagnosis and Management of Urinary Tract Infection in Older Adults

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Definition of common terms

Pyuria	>10 white blood cells (WBC)/mm^3 per high-power field (HPF)
Bacteriuria	Urinary pathogen of $\geq 10^5$ colony-forming units (cfu) per mL
Laboratory-confirmed UTI	Pyuria (>10 WBC/mm^3 per HPF) plus bacteriuria ($\geq 10^5$ cfu/mL)
Asymptomatic bacteriuria	Bacteriuria in the absence of genitourinary signs or symptoms
Symptomatic UTI	Bacteriuria in the presence of genitourinary symptoms (ie, dysuria, suprapubic pain or tenderness, frequency, or urgency)
Uncomplicated UTI	Genitourinary symptoms (ie, dysuria, suprapubic pain or tenderness, frequency, or urgency) with evidence of pyuria plus bacteriuria in a structurally normal urinary tract
Complicated UTI	UTI occurring in a patient with a structural or functional urinary tract abnormality

Diagnosis and Management of Urinary Tract Infection in Older Adults. Infect Dis Clin North Am. 2014 March ; 28(1): 75–89.

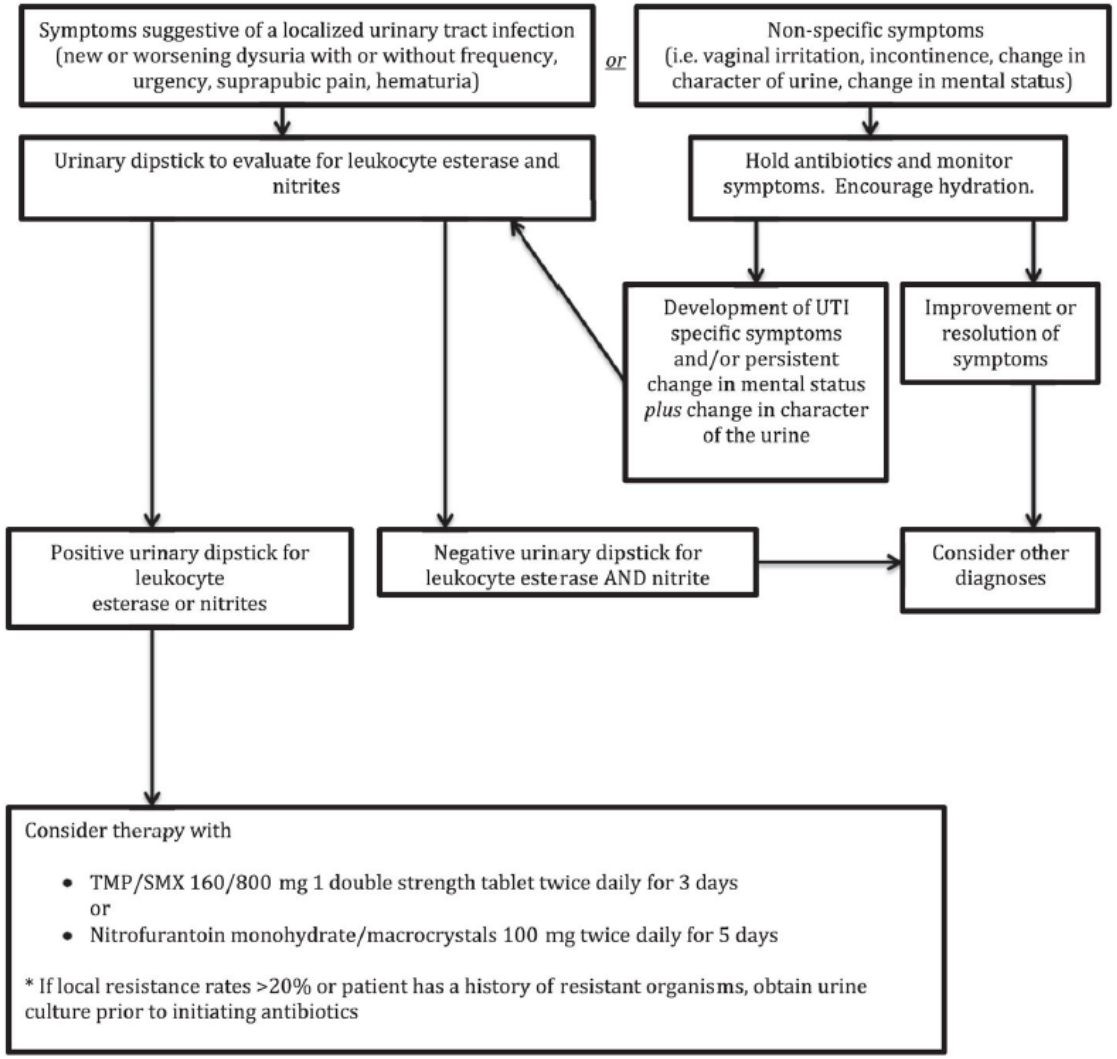

Fig. 2.
Proposed diagnostic and empiric treatment algorithm for UTI in community-dwelling older adults.

Diagnosis and Management of Urinary Tract Infection in Older Adults. Infect Dis Clin North Am. 2014 March ; 28(1): 75–89.

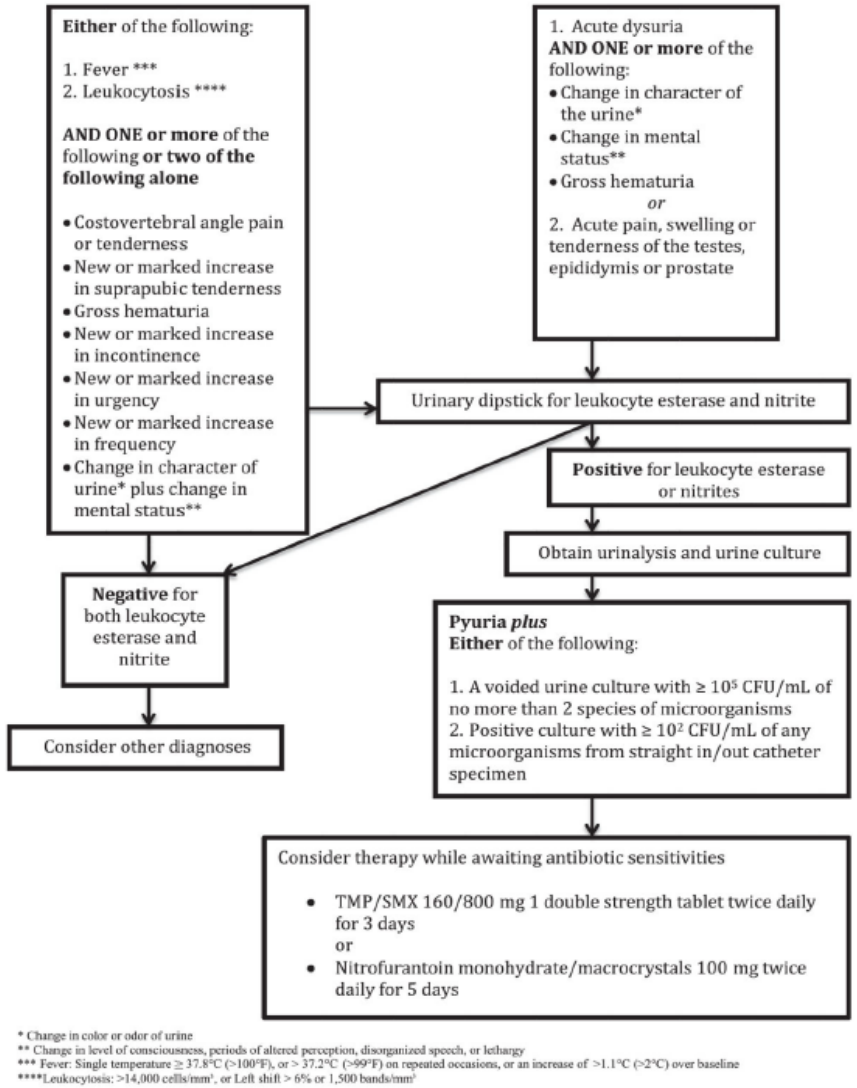

Fig. 3.
Proposed diagnostic algorithm for UTI in long-term care facilities for residents without an indwelling catheter.

Diagnosis and Management of Urinary Tract Infection in Older Adults. Infect Dis Clin North Am. 2014 March ; 28(1): 75–89.

Published in final edited form as:
Infect Control Hosp Epidemiol. 2012 October ; 33(10): 965–977. doi:10.1086/667743.

Surveillance Definitions of Infections in Long-Term Care Facilities: Revisiting the McGeer Criteria

Nimalie D. Stone, MD[1], Muhammad S. Ashraf, MD[2], Jennifer Calder, PhD[3], Christopher J. Crnich, MD[4], Kent Crossley, MD[5], Paul J. Drinka, MD[6], Carolyn V. Gould, MD[1], Manisha Juthani-Mehta, MD[7], Ebbing Lautenbach, MD[8], Mark Loeb, MD[9], Taranisia MacCannell, PhD[1], Preeti N. Malani, MD[10,11], Lona Mody, MD[10,11], Joseph M. Mylotte, MD[12], Lindsay E. Nicolle, MD[13], Mary-Claire Roghmann, MD[14], Steven J. Schweon, MSN[15], Andrew E. Simor,

Surveillance Definitions for Urinary Tract Infections (UTIs)

Criteria	Comments
A. For residents without an indwelling catheter (both criteria 1 and 2 must be present) 1. At least 1 of the following sign or symptom subcriteria **a.** Acute dysuria or acute pain, swelling, or tenderness of the testes, epididymis, or prostate **b.** Fever or leukocytosis (see Table 2) and at least 1 of the following localizing urinary tract subcriteria **i.** Acute costovertebral angle pain or tenderness **ii.** Suprapubic pain **iii.** Gross hematuria **iv.** New or marked increase in incontinence **v.** New or marked increase in urgency **vi.** New or marked increase in frequency **c.** In the absence of fever or leukocytosis, then 2 or more of the following localizing urinary tract subcriteria **i.** Suprapubic pain **ii.** Gross hematuria **iii.** New or marked increase in incontinence **iv.** New or marked increase in urgency **v.** New or marked increase in frequency	UTI should be diagnosed when there are localizing genitourinary signs and symptoms and a positive urine culture result. A diagnosis of UTI can be made without localizing symptoms if a blood culture isolate is the same as the organism isolated from the urine and there is no alternate site of infection. In the absence of a clear alternate source of infection, fever or rigors with a positive urine culture result in the noncatheterized resident or acute confusion in the catheterized resident will often be treated as UTI. However, evidence suggests that most of these episodes are likely not due to infection of a urinary source.
2. One of the following microbiologic subcriteria **a.** At least 10^5 cfu/mL of no more than 2 species of microorganisms in a voided urine sample **b.** At least 10^2 cfu/mL of any number of organisms in a specimen collected by in-and-out catheter	Urine specimens for culture should be processed as soon as possible, preferably within 1–2 h. If urine specimens cannot be processed within 30 min of collection, they should be refrigerated. Refrigerated specimens should be cultured within 24 h.

Surveillance Definitions of Infections in Long-Term Care Facilities: Revisiting the McGeer Criteria. *Infect Control Hosp Epidemiol.* 2012 October ; 33(10): 965–977.

Surveillance Definitions for Urinary Tract Infections (UTIs)

Criteria	Comments
B. For residents with an indwelling catheter (both criteria 1 and 2 must be present)	Recent catheter trauma, catheter obstruction, or new-onset hematuria are useful localizing signs that are consistent with UTI but are not necessary for diagnosis.
1. At least 1 of the following sign or symptom subcriteria	
a. Fever, rigors, or new-onset hypotension, with no alternate site of infection	
b. Either acute change in mental status or acute functional decline, with no alternate diagnosis and leukocytosis	
c. New-onset suprapubic pain or costovertebral angle pain or tenderness	
d. Purulent discharge from around the catheter or acute pain, swelling, or tenderness of the testes, epididymis, or prostate	
2. Urinary catheter specimen culture with at least 10^5 cfu/mL of any organism(s)	Urinary catheter specimens for culture should be collected following replacement of the catheter (if current catheter has been in place for >14 d).

NOTE. Pyuria does not differentiate symptomatic UTI from asymptomatic bacteriuria. Absence of pyuria in diagnostic tests excludes symptomatic UTI in residents of long-term care facilities. cfu, colony-forming units.

Surveillance Definitions of Infections in Long-Term Care Facilities: Revisiting the McGeer Criteria. *Infect Control Hosp Epidemiol.* 2012 October ; 33(10): 965–977.

4

Clinical Review & Education

JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Screening for Atrial Fibrillation
US Preventive Services Task Force Recommendation Statement

JAMA. 2022;327(4):360-367.

US Preventive Services Task Force

IMPORTANCE Atrial fibrillation (AF) is the most common cardiac arrhythmia. The prevalence of AF increases with age, from less than 0.2% in adults younger than 55 years to about 10% in those 85 years or older, with a higher prevalence in men than in women. It is uncertain whether the prevalence of AF differs by race and ethnicity. Atrial fibrillation is a major risk factor for ischemic stroke and is associated with a substantial increase in the risk of stroke. Approximately 20% of patients who have a stroke associated with AF are first diagnosed with AF at the time of the stroke or shortly thereafter.

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IMPORTANCE:

- Atrial fibrillation (AF) is the **most common** cardiac arrhythmia.
- **Prevalence increases with age**,
  (< 0.2%in adults < 55 years to 10% in ≥ 85 years)
- **Higher prevalence in men** than in women.
- Atrial fibrillation is a **major risk factor for ischemic stroke**.
- Approximately **20%** of patients who have a stroke associated with AF are **first diagnosed** with AF **at the time of the stroke** or shortly thereafter.

USPSTF 2018:

In 2018, the USPSTF concluded that the **evidence was insufficient to assess the balance of benefits and harms of using ECG to screen for AF**.

USPSTF 2021 UPDATE:

This 2021 evidence review included searching for evidence on **additional screening methods such as automated blood pressure cuffs, pulse oximeters, and consumer devices such as smartwatches and smartphone apps**.

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

REFERENCE: https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/grade-definitions

POPULATION: Adults 50 years or older without a diagnosis or symptoms of AF and without a history of transient ischemic attack or stroke.

Table. Summary of USPSTF Rationale

Rationale	Assessment
Detection	• Inadequate evidence to assess whether 1-time screening strategies identify adults 50 years or older with previously undiagnosed AF more effectively than usual care. • Adequate evidence that intermittent and continuous screening strategies identify adults 50 years or older with previously undiagnosed AF more effectively than usual care.
Benefits of early detection and intervention and treatment	• Inadequate direct evidence on the benefits of screening for AF. • Inadequate evidence on the benefits of treatment of screen-detected AF, particularly paroxysmal AF of short duration.
Harms of early detection and intervention and treatment	• Inadequate direct evidence on the harms of screening for AF. • Adequate evidence that treatment of AF with anticoagulant therapy is associated with small to moderate harm, particularly an increased risk of major bleeding.
USPSTF assessment	Evidence is lacking, and the balance of benefits and harms of screening for AF in asymptomatic adults cannot be determined.

Abbreviations: AF, atrial fibrillation; USPSTF, US Preventive Services Task Force.

USPSTF 2021:

The USPSTF **concludes** that the current **evidence is insufficient** to assess the balance of benefits and harms of screening for AF. (**I statement**)

JAMA Cardiol. 2022; 7(3):247-249.

EDITORIAL

Updated USPSTF Guidelines for Screening for Atrial Fibrillation
Same as It Ever Was?

Rod Passman, MD, MSCE; Ben Freedman, MBBS, PhD

Five decades of research have illuminated the role of nonvalvular atrial fibrillation (AF) in the pathogenesis of stroke, heart failure, dementia, and premature death. Given the often-asymptomatic nature of the arrhythmia and the clear benefit of premorbid interventions including anticoagulation for stroke prevention, it makes intuitive sense that screening for asymptomatic AF would affect outcomes. However, the evidence to support screening remains elusive.[7,8] Still, ECG remains the criterion standard for diagnosing AF, although it too can be misinterpreted and may trigger additional and often unnecessary testing owing to other abnormal findings even if the rhythm is normal.

Regardless of how the diagnosis is made, for AF screening to be fully endorsed, it must first be demonstrated that screen-detected AF carries the same prognosis and responds similarly to interventions as clinically detected AF. Data from recent retrospective studies support both these requirements. Compared with symptomatic patients with AF in the Global Anticoagulant Registry in the Field-Atrial Fibrillation (GARFIELD-AF) study,[9] those who were asymptomatic at the

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EDITORIAL

The **historical focus** of the AF screening debate has been on the **utility of screening initiated by health care professionals** using pulse palpation and/or ECG recordings.

The **advent of direct-to-consumer, smartphone-based devices** capable of assessing pulse regularity using photoplethysmography or recording a single-lead ECG **has changed the paradigm of how and where screening can be performed**.

These advances will likely highlight **the trade-off of continuous monitoring strategies that provide increased detection of lower-burden AF representing a lower risk of stroke that may not benefit from anticoagulation**. To be effective, the movement toward consumer-based screening must first show that such an approach improves outcomes. It must also deal with the **paradox that those at highest risk of AF and AF-related stroke may be the least likely to own these technologies unless supported by the health care system**.

JAMA Network Open™

JAMA Network Open. 2022; 5(1):e2139910.

Editorial

Screening for Atrial Fibrillation—Refining the Target

Matthew M. Kalscheur, MD; Zachary D. Goldberger, MD, MS

Atrial fibrillation (AF) profoundly affects individual patients and the health system at large. The substantial morbidity, mortality, and health-related expenditures associated with this exceedingly common arrhythmia cannot be underestimated.[1] Indeed, the association between AF and increased risk of stroke (often debilitating) is well established.[2]

As such, screening for AF is of paramount interest to public health. In 2018, the US Preventive Services Task Force (USPSTF) found that available evidence was insufficient to assess the balance of

AF lies along a spectrum of importance; **assessing the burden of AF, rather than the presence or absence, may be a better approach.**

In the LOOP trial, which enrolled approximately 6000 older patients without AF with a median CHA2DS2-VASc score of 4 and randomized them to implantable loop recorder (ILR) monitoring or usual outpatient care, the **nearly 3-fold increase in both AF detection and anticoagulation use with ILRs (which are costly) did not translate into improved outcomes** in individuals at exceedingly high risk of stroke.

The potential benefits of early AF detection should extend beyond stroke prevention. Attempts at disease modification through behavior and lifestyle modification are of paramount importance. **Patients identified with AF likely would benefit from targeted management of modifiable risk factors that contribute to AF, including obesity, hypertension, alcohol use, sleep apnea, smoking, and diabetes.** Future studies should focus on structured, patient specific behavior interventions.

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DOI: 10.1111/jgs.17886

Journal of the
American Geriatrics Society

Cognitive impairment, age, quality of life, and treatment strategy for atrial fibrillation in older adults: The SAGE-AF study

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[2]Bouvé College of Health Sciences,

Abstract

Background: Atrial fibrillation (AF) treatment includes anticoagulation for high stroke risk individuals and either rate or rhythm control strategies. We aimed to investigate the impact of age, geriatric factors, and medical com-

METHODS:

Patients with AF aged ≥65 years with CHA2DS2VASc score ≥2 and eligible for anticoagulation [Systematic Assessment of Geriatric Elements-AF **(SAGE-AF) prospective cohort study**]

RESULTS:

1244 participants (mean age 76 years; 49% female; 85% non-Hispanic white)

Rate and rhythm control were used in 534 and 710 participants, respectively.

Those ≥75 were more likely to be treated with a rate control strategy; have cognitive impairment and peripheral vascular disease (PVD) but less likely to have visual impairment, congestive heart failure or receive anticoagulation.

CONCLUSION:

Older age, cognitive impairment, and PVD were associated with use of rate control strategy.

Visual impairment, CHF, and anticoagulation use were associated with a rhythm control strategy.

There was no difference in HRQoL between the rate and rhythm control groups.

Received: 5 February 2022 | Revised: 9 May 2022 | Accepted: 8 June 2022

DOI: 10.1111/jgs.17954

Journal of the
American Geriatrics Society

Perception of atrial fibrillation symptoms: Impact on quality of life and treatment in older adults

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Abstract

Background: In managing older adults with atrial fibrillation (AF), their symptomatology impacts their well-being and may inform treatment decision-

METHODS:

[Systematic Assessment of Geriatric Elements-AF **(SAGE-AF) prospective cohort study**]

Three age groups:

- 65–74 (youngest–old),
- 75–84 (middle–old), and
- ≥85 (oldest)

Perception of AF symptoms:

Atrial Fibrillation Effect on Quality-of-Life Questionnaire

Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) Questionnaire

Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) Questionnaire

Section 1. Occurrence of atrial fibrillation **Name or ID:**_____

Are you currently in atrial fibrillation? ☐ Yes ☐ No

If **No**, when was the last time you were aware of having had an episode of atrial fibrillation? (Please check one answer which best describes your situation)

__earlier today
__within the past week
__within the past month
__1 month to 1 year ago
__more than 1 year ago
__I was never aware of having atrial fibrillation

Section 2. The following questions refer to how atrial fibrillation affects your quality of life.

On a scale of 1 to 7, over the past 4 weeks, as a result of your atrial fibrillation, how much were you bothered by: (Please circle one number which best describes your situation)

	Not at all bothered Or I did not have this symptom	Hardly bothered	A little bothered	Moderately bothered	Quite a bit bothered	Very bothered	Extremely bothered
1. Palpitations: Heart fluttering, skipping or racing	1	2	3	4	5	6	7
2. Irregular heart beat	1	2	3	4	5	6	7
3. A pause in heart activity	1	2	3	4	5	6	7
4. Lightheadedness or dizziness	1	2	3	4	5	6	7

On a scale of 1 to 7, over the past 4 weeks, have you been limited by your atrial fibrillation in your: (Please circle one number which best describes your situation)

	Not at all limited	Hardly limited	A little limited	Moderately limited	Quite a bit limited	Very limited	Extremely limited
5. Ability to have recreational pastimes, sports, and hobbies	1	2	3	4	5	6	7
6. Ability to have a relationship and do things with friends and family	1	2	3	4	5	6	7

On a scale of 1 to 7, over the past 4 weeks, as a result of your atrial fibrillation, how much difficulty have you had in: (Please circle one number which best describes your situation)

	No difficulty at all	Hardly any difficulty	A little difficulty	Moderate difficulty	Quite a bit of difficulty	A lot of difficulty	Extreme difficulty
7. Doing any activity because you felt tired, fatigued, or low on energy	1	2	3	4	5	6	7
8. Doing physical activity because of shortness of breath	1	2	3	4	5	6	7
9. Exercising	1	2	3	4	5	6	7
10. Walking briskly	1	2	3	4	5	6	7
11. Walking briskly uphill or carrying groceries or other items, up a flight of stairs without stopping	1	2	3	4	5	6	7
12. Doing vigorous activities such as lifting or moving heavy furniture, running, or participating in strenuous sports like tennis or racquetball	1	2	3	4	5	6	7

Developed by AFEQT Core Team-John Spertus, MD, Mid America Heart Institute, Kansas City, MO; Paul Dorian, MD, St. Michaels Hospital, Toronto, ON; Rosemary Bubien, RN, University of Alabama, Birmingham, AL; Caroline Burk, Pharm D. M.S; Steven Lewis, PhD; Donna Godejohn, BSN, St. Jude Medical, St. Paul, MN.

Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) Questionnaire

On a scale of 1 to 7, over the past 4 weeks as a result of your atrial fibrillation, how much did the feelings below bother you? (Please circle one number which best describes your situation)

	Not at all Bothered	Hardly bothered	A little bothered	Moderately bothered	Quite a bit bothered	Very bothered	Extremely bothered
13. Feeling worried or anxious that your atrial fibrillation can start anytime	1	2	3	4	5	6	7
14. Feeling worried that atrial fibrillation may worsen other medical conditions in the long run	1	2	3	4	5	6	7

On a scale of 1 to 7, over the past 4 weeks, as a result of your atrial fibrillation treatment, how much were you bothered by: (Please circle one number which best describes your situation)

	Not at all bothered	Hardly bothered	A little bothered	Moderately bothered	Quite a bit bothered	Very bothered	Extremely bothered
15. Worrying about the treatment side effects from medications	1	2	3	4	5	6	7
16. Worrying about complications or side effects from procedures like catheter ablation, surgery, or pacemakers therapy	1	2	3	4	5	6	7
17. Worrying about side effects of blood thinners such as nosebleeds, bleeding gums when brushing teeth, heavy bleeding from cuts, or bruising.	1	2	3	4	5	6	7
18. Worrying or feeling anxious that your treatment interferes with your daily activities	1	2	3	4	5	6	7

On a scale of 1 to 7, overall, how satisfied are you **at the present time** with: (Please circle one number which best describes your situation)

	Extremely satisfied	Very satisfied	Somewhat satisfied	Mixed with satisfied and dissatisfied	Somewhat dissatisfied	Very dissatisfied	Extremely dissatisfied
19. How well your current treatment controls your atrial fibrillation?	1	2	3	4	5	6	7
20. The extent to which treatment has relieved your symptoms of atrial fibrillation?	1	2	3	4	5	6	7

Name or ID:_____

Version 1.0 © 2009 St. Jude Medical, Inc. All Rights Reserved License Required for Use
Developed by AFEQT Core Team-John Spertus, MD, Mid America Heart Institute, Kansas City, MO; Paul Dorian, MD, St. Michaels Hospital, Toronto, ON; Rosemary Bubien, RN, University of Alabama, Birmingham, AL; Caroline Burk, Pharm D. M.S; Steven Lewis, PhD; Donna Godejohn, BSN, St. Jude Medical, St. Paul, MN.

http://www.afeqt.org/files/AFEQT_Questionnaire.pdf

RESULTS:

1184 participants (mean age 75 years, 48% women, 86% Non-Hispanic White), 51% were aged 65–74 years, 36% were 75–84 years, and 13% were ≥ 85 years.

Most commonly reported AF symptoms were non-specific, non-cardiac symptoms (fatigue, dyspnea, lightheadedness).

Cardiac-specific AF symptoms (palpitations, irregular heartbeat, pause in heart activity) **were less prevalent, but most commonly reported by the youngest participants (65–74 years)**.

Overall, **those who reported experiencing any AF symptoms were more likely to have received rhythm** compared with rate **control** with similar findings for all age groups except those aged ≥85 years.

CONCLUSIONS:

High prevalence of non-specific, noncardiac symptoms among older adults with AF

Cardiac-specific AF symptoms may exert considerable impact on QoL

Presence of any AF symptoms may drive more rhythm control in a majority of older adults

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Silence is gilded: Atrial fibrillation in the golden years

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a prevalence of 9% among older adults age 80–89 years.[1,2] It may cause significant morbidity and mortality, and older age is a known risk factor for the development of AF.[3] Clinicians may manage AF with rhythm control using electrical cardioversion, left atrial ablation, anti-arrhythmic medications, or rate control, how older adults experience symptoms and perceive QoL with AF. The authors reviewed AF symptoms in patients according to age groups (65–74, 75–84, and 85 and above) using comprehensive survey data and a validated tool assessing AF symptoms and related QoL. The cohort, drawn from the multi-center Systematic Assessment of Geriatric Elements in AF (SAGE-AF) study, included 1184 participants with a mean age of 75 years.

In this study, patients were administered the vali-

EDITORIAL:

The **oldest group was less likely to report decreased QoL**, and believe that these individuals **may have learned to cope with their illness in comparison to the younger group**, which was **seemingly more bothered by their symptoms**.

As an alternative explanation, the **oldest group may have more comorbidities to which they attribute symptoms**, while the **younger group may be more likely to point to AF as the cause of their symptoms** if they had fewer medical conditions.

Incorporation of the validated AFEQT questionnaire into practice may be helpful for clinicians to discern symptom burden.

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Research

JAMA Cardiology | Original Investigation

JAMA Cardiol. 2022;7(3):250-256.

Association of Apolipoprotein B–Containing Lipoproteins and Risk of Myocardial Infarction in Individuals With and Without Atherosclerosis

Distinguishing Between Particle Concentration, Type, and Content

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IMPORTANCE Lipid management typically focuses on levels of low-density lipoprotein cholesterol (LDL-C) and, to a lesser extent, triglycerides (TG). However, animal models and genetic studies suggest that the atherogenic particle subpopulations (LDL and very-low-density lipoprotein [VLDL]) are both important and that the number of particles is more predictive of cardiac events than their lipid content.

Invited Comm

Supplemental

INTRODUCTION

Lipids such as cholesterol are insoluble in plasma and for delivery to tissues, **have to be packaged into lipoproteins.**

Apolipoprotein B (ApoB) is the primary apolipoprotein and is the carrier for the following lipids: chylomicrons, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), intermediate density lipoprotein (IDL), and lipoprotein (a). It also serves as the primary ligand for LDL receptor mediated clearance of LDL particles from the blood.

ApoB is a large protein that envelops the surface of atherogenic lipoproteins as a macromolecular scaffold to provide structural integrity. **The apoB molecule** is present in a defined stoichiometry, **one single copy per particle.**

There are two circulating forms of Apo B, Apo B48 (from the small intestine with molecular mass 48% of hepatic ApoB) **and Apo B100 (from the liver).**

https://www.ncbi.nlm.nih.gov/books/NBK538139/?report=classic

METHODS

Study Design and Population

Prospective cohort analysis in **2 types of patient populations**.

The **primary prevention group included 389,529 individuals without lipid-lowering therapy** from a general population in UK Biobank. **Median age 56 yrs; more females**

The **second group included 40, 430 patients with established atherosclerosis disease who were receiving lipid-lowering therapy** and were enrolled in either Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) or Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT). **Median age 63 yrs; more males**

The **median follow-up was 11.1 years in UK Biobank and 2.5 years in the clinical trials**.

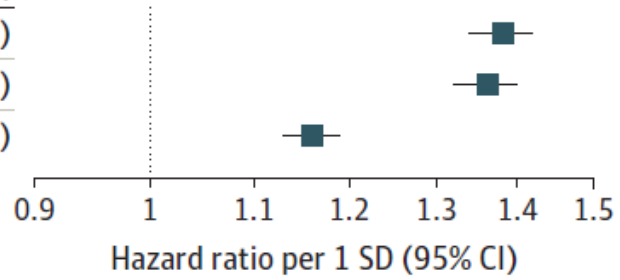
End Points

The end point of interest in both cohorts was **fatal or nonfatal MI**.

Figure 1. Lipid Parameters and Risk of Myocardial Infarction

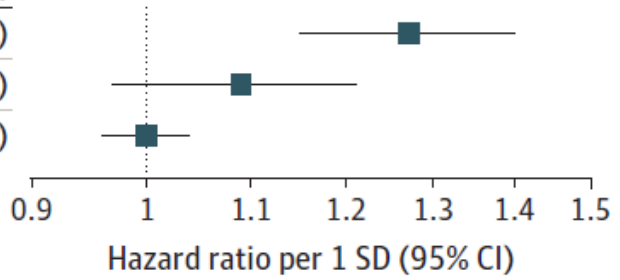
A Primary prevention: clinically adjusted

Lipid parameter	Hazard ratio per 1 SD (95% CI)
Apo B	1.38 (1.34-1.42)
Non-HDL-C	1.36 (1.32-1.40)
TG	1.16 (1.13-1.19)



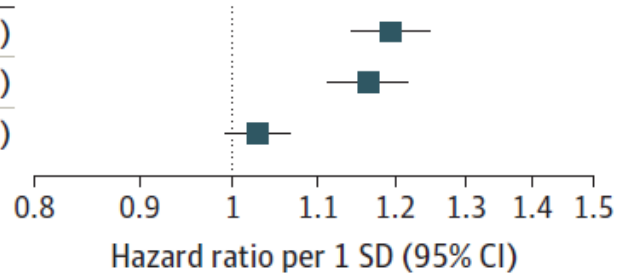
B Primary prevention: clinically and lipid adjusted

Lipid parameter	Hazard ratio per 1 SD (95% CI)
Apo B	1.27 (1.15-1.40)
Non-HDL-C	1.09 (0.97-1.21)
TG	1.00 (0.96-1.04)



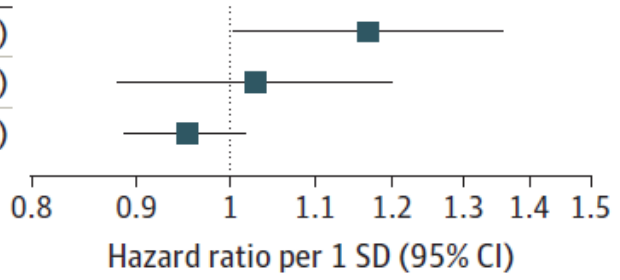
C Secondary prevention: clinically adjusted

Lipid parameter	Hazard ratio per 1 SD (95% CI)
Apo B	1.19 (1.14-1.25)
Non-HDL-C	1.16 (1.11-1.22)
TG	1.03 (0.99-1.07)



D Secondary prevention: clinically and lipid adjusted

Lipid parameter	Hazard ratio per 1 SD (95% CI)
Apo B	1.17 (1.00-1.36)
Non-HDL-C	1.03 (0.88-1.20)
TG	0.94 (0.89-1.00)



RESULTS

3 key findings

First, **apoB was the only independent driver of lipid-associated MI risk**, confirming the importance of particle concentration.

Second, the **amount of lipid** (cholesterol or TG) carried on the apoB-containing lipoprotein particles **did not confer additional risk** beyond apoB concentration.

Third, the **type of apoB-containing lipoprotein particle**, either TG-rich lipoproteins or LDL particle, **did not confer additional risk** beyond particle concentration.

Each of these findings was consistent across both primary and secondary populations and in those receiving and not receiving lipid lowering therapy.

CONCLUSIONS

In this cohort study, **association with MI was best captured by the number of apoB-containing lipoproteins**, **independent from lipid content (cholesterol or TG) or type of lipoprotein (LDL or TG-rich)**.

This suggests that **apoB may be the primary driver of atherosclerosis** and that lowering the overall concentration of all apoB-containing lipoproteins should be the focus of therapeutic strategies.

COMMENTARY

When necessary, **non–HDL-C in particular is the preferred surrogate for apoB**, as it incorporates TG-rich lipoproteins in addition to LDL.

There is also **still value in the traditional lipid panel in understanding what is driving a high concentration of apoB containing lipoproteins**. For example, very high LDL-C but normal TGs could suggest familial hypercholesterolemia, whereas very high TGs and normal LDL-C are more consistent with a primary hypertriglyceridemia.

This knowledge could impact the clinical diagnosis, choice of lipid-lowering therapy, and need for genetic testing and family screening. **Therefore, apoB should not replace the standard lipid panel, but rather be added to it when possible.**

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Clinical Review & Education

JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

JAMA. 2022;328(8):746-753.

Statin Use for the Primary Prevention of Cardiovascular Disease in Adults
US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

IMPORTANCE Cardiovascular disease (CVD) is the leading cause of morbidity and death in the US and is the cause of more than 1 of every 4 deaths. Coronary heart disease is the single leading cause of death and accounts for 43% of deaths attributable to CVD in the US. In 2019, an estimated 558 000 deaths were caused by coronary heart disease and 109 000 deaths were caused by ischemic stroke.

OBJECTIVE To update its 2016 recommendation, the US Preventive Services Task Force (USPSTF) commissioned a review of the evidence on the benefits and harms of statins for reducing CVD-related morbidity or mortality or all-cause mortality.

Editorial page 716

Multimedia

Related article page 754 and
JAMA Patient Page page 786

Supplemental content

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jamacardiology.com
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jamanetworkopen.com

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

REFERENCE: https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/grade-definitions

USPSTF 2016:

Figure 2. Statin Use for the Primary Prevention of CVD in Adults: Clinical Summary

Population	Adults aged 40–75 y with no history of CVD, ≥1 CVD risk factors, and calculated 10-y CVD event risk ≥10%	Adults aged 40–75 y with no history of CVD, ≥1 CVD risk factors, and calculated 10-y CVD event risk of 7.5%–10%	Adults 76 y and older with no history of CVD
Recommendation	Initiate use of low- to moderate-dose statins. Grade: B	Discuss with patient and selectively offer use of low- to moderate-dose statins. Grade: C	No recommendation. Grade: I (insufficient evidence)

USPSTF 2021 UPDATE

Population	Recommendation	Grade
Adults aged 40 to 75 years who have 1 or more cardiovascular risk factors and an estimated 10-year cardiovascular disease (CVD) risk of 10% or greater	The USPSTF recommends that clinicians prescribe a statin for the primary prevention of CVD for adults aged 40 to 75 years who have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking) and an estimated 10-year risk of a cardiovascular event of 10% or greater.	B
Adults aged 40 to 75 years who have 1 or more cardiovascular risk factors and an estimated 10-year CVD risk of 7.5% to less than 10%	The USPSTF recommends that clinicians selectively offer a statin for the primary prevention of CVD for adults aged 40 to 75 years who have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking) and an estimated 10-year risk of a cardiovascular event of 7.5% to less than 10%. The likelihood of benefit is smaller in this group than in persons with a 10-year risk of 10% or greater.	C
Adults 76 years or older	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of initiating a statin for the primary prevention of CVD events and mortality in adults 76 years or older.	I

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JACC. 2022, Vol 80: No. 14:1366-1418.

EXPERT CONSENSUS DECISION PATHWAY

2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

A Report of the American College of Cardiology Solution Set Oversight Committee

Endorsed by the National Lipid Association

POPULATION GROUPS

Adults With Clinical ASCVD **at Very High Risk** on Statin Therapy for Secondary Prevention

Adults With Clinical ASCVD, **Not at Very High Risk**, on Statin Therapy for Secondary Prevention

Adults With Clinical ASCVD and **Baseline LDL-C ≥190 mg/dL** Not Due to Secondary Causes **Without Clinical or Genetic Diagnosis of Familial Hypercholesterolemia**, on Statin Therapy for Secondary Prevention

Adults With Clinical ASCVD at Very High Risk and **Baseline LDL-C ≥190 mg/dL** Not Due to Secondary Causes and **With Clinical Diagnosis or Genetic Confirmation of Familial Hypercholesterolemia**, on Statin for Secondary Prevention

POPULATION GROUPS

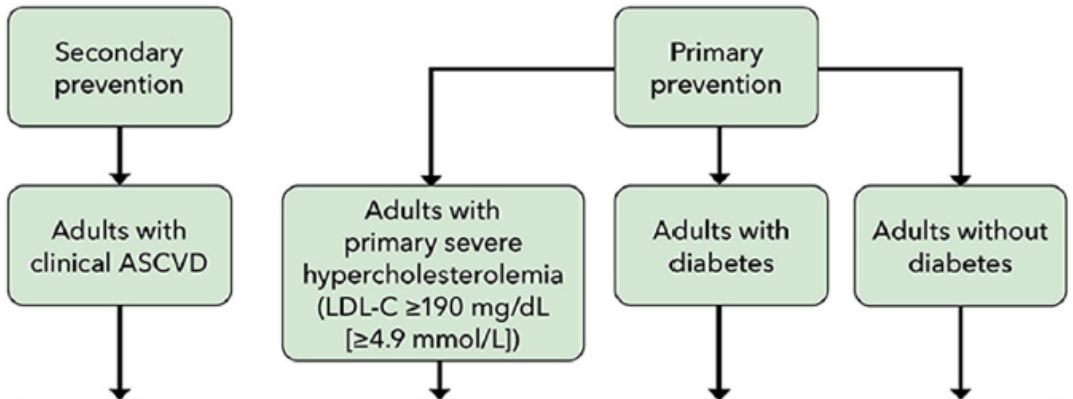
Adults **Without Clinical ASCVD** and With Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes on Statin Therapy for **Primary Prevention**

Adults **With Diabetes** and Without ASCVD and Baseline **LDL-C <190 mg/dL** on Statin Therapy for **Primary Prevention**

Adults **Without Clinical ASCVD or Diabetes (LDL 70-189 mg/dL)**

Adults With **Possible Statin-Associated Side Effects**

PATIENT MANAGEMENT GROUPS



FACTORS TO CONSIDER:

- Adherence to lifestyle modifications and adherence to evidence-based, guideline-recommended statin therapy
- Patient on guideline-recommended statin therapy
- Risk-enhancing factors
- Control of other risk factors
- Clinician-patient decision about the potential benefits, potential harms, and patients preferences with regard to the addition of nonstatin therapies
- Percentage LDL-C reduction and absolute LDL-C or non-HDL-C level achieved
- Monitoring of response to lifestyle modifications, adherence, and therapy
- Cost of therapy
- Statin-associated side effects
- Persistent hypertriglyceridemia

OPTIONAL INTERVENTIONS TO CONSIDER IN APPROPRIATE PATIENT GROUPS:

- Referral to a lipid specialist and registered dietitian/registered dietitian nutritionist
- Ezetimibe
- Bile acid sequestrants
- PCSK9 mAbs*
- Bempedoic acid
- Inclisiran
- LDL apheresis may be considered by lipid specialist for patients with familial hypercholesterolemia
- Lomitapide (only in HoFH)
- Evinacumab (only in HoFH)

*PCSK9 mAb includes alirocumab and evolocumab. ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 mAb = proprotein convertase subtilisin/kexin type 9 monoclonal antibodies.

(newer) Non-statin Therapies for Cholesterol Lowering

- **Evolocumab (Repatha)**
- **Alirocumab (Praluent)**
- Proprotein convertase subtilisin/kexin type 9 monoclonal antibodies (PCSK9ab)
- Inhibit PCSK9 binding to LDL receptors, decreasing LDL receptor degradation and increasing LDL clearance
- Admn: SQ; q 2 wks or q mth

- **Bempedoic acid (Nexletol)**
- Inhibits adenosine triphosphate-citrate lyase (ACL), inhibiting cholesterol synthesis
- Admn: p.o. once daily

- **Inclisiran (Leqvio)**
- Small interfering ribonucleic acid (siRNA) directs catalytic breakdown of mRNA for PCSK9 synthesis and subsequent binding to LDL receptors, increasing LDL receptor recycling and decreasing circulating LDL
- Admn: SQ; q 6 mths

- **Lomitapide (Juxtapid)**
- (restricted distribution in U. S.)
- Inhibits microsomal triglyceride transfer protein (MTP), decreasing production of chylomicrons and VLDL
- Admn: p.o. once daily

- **Evinacumab (Evkeeza)**
- Inhibits angiopoietin-like 3 (ANGPTL3), increasing lipid metabolism and decreasing LDL-C, HDL-C, and triglycerides (monoclonal antibody)
- Admn: IV q 4 wks

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ESC European Society of Cardiology

European Heart Journal (2022) **43**, 2010–2019
https://doi.org/10.1093/eurheartj/ehac179

FASTTRACK CLINICAL RESEARCH
Clinical trials

European Heart Journal (2022) 43, 2010–2019.

Effects of aspirin on dementia and cognitive function in diabetic patients: the ASCEND trial

Sarah Parish [1,2*†], Marion Mafham [2†], Alison Offer [2], Jill Barton [2], Karl Wallendszus [2], William Stevens [2], Georgina Buck [2], Richard Haynes [2], Rory Collins [2‡], Louise Bowman [1,2‡], and Jane Armitage [1,2‡], on behalf of the ASCEND Study Collaborative Group

[1]MRC Population Health Research Unit, Nuffield Department of Population Health, University of Oxford, Big Data Institute, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, UK; and [2]Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK

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See the editorial comment for this article 'The end of aspirin for dementia prevention in diabetes?', by Steen D. Kristensen *et al.*, https://doi.org/10.1093/eurheartj/ehac211.

METHODS

In the ASCEND trial, about **15,000 people from the UK with diabetes and no history of cardiovascular disease or dementia were randomized to aspirin 100 mg daily** or matching placebo for a **mean of 7.4 years**.

Primary pre-specified outcome = 'broad dementia', comprising dementia, cognitive impairment, or confusion. (ascertained through participant, carer, or general practitioner report or hospital admission diagnosis).

RESULTS

The broad dementia outcome occurred in a similar percentage of participants in the aspirin group and placebo group: 548 participants (7.1%) vs. 598 (7.8%).

CONCLUSION

Aspirin does not have a large proportional effect on the risk of dementia.

European Heart Journal (2022) 43, 2020–2022.

ESC European Society of Cardiology

European Heart Journal (2022) **43**, 2020–2022
https://doi.org/10.1093/eurheartj/ehac211

EDITORIAL

The end of aspirin for dementia prevention in diabetes?

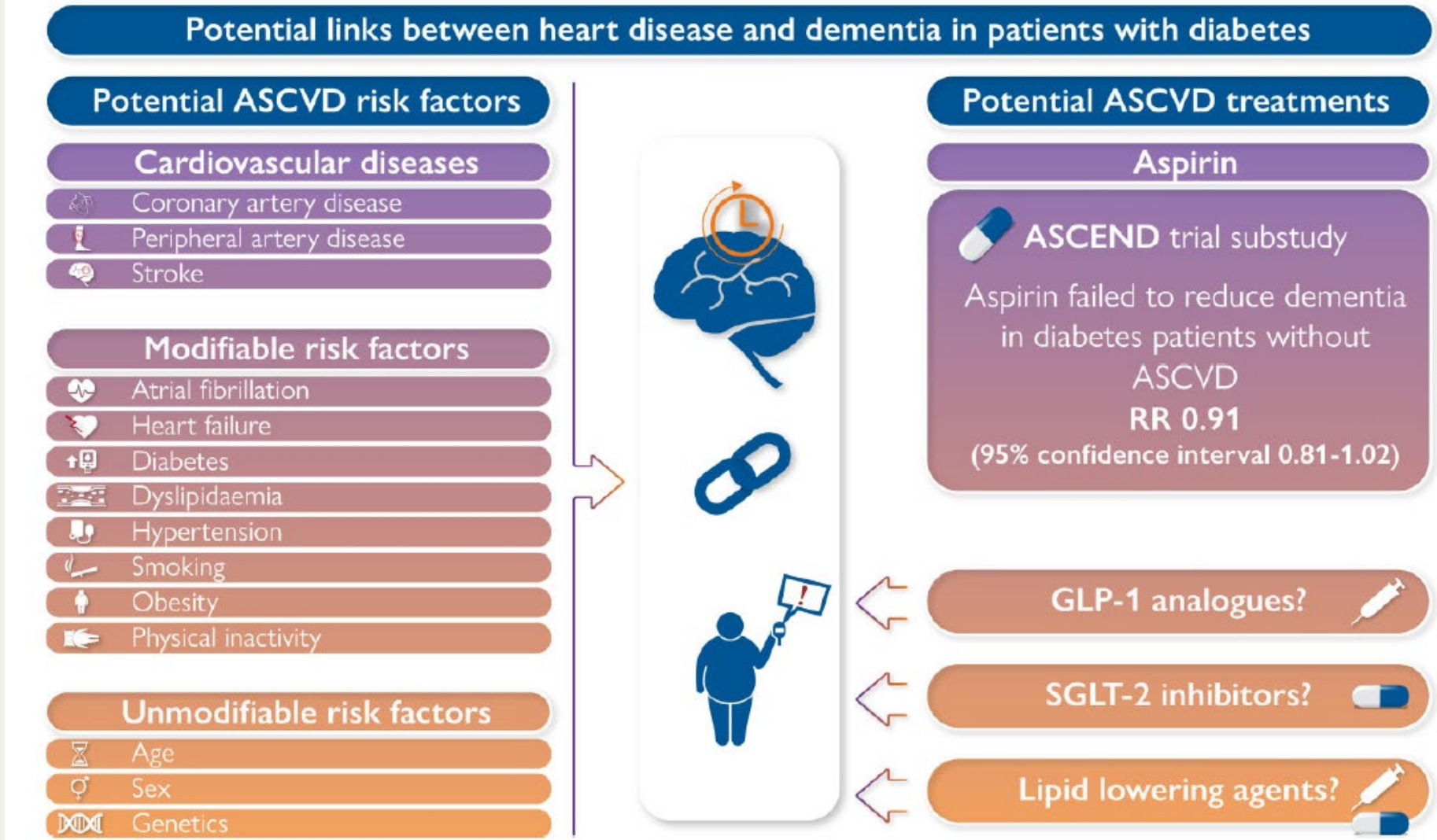
Steen D. Kristensen[1,2]*, Kevin K.W. Olesen[1], and Michael Maeng[1,2]

[1]Department of Cardiology, Aarhus University Hospital, Aarhus N, Denmark; and [2]Institute of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus N, Denmark

Online publish-ahead-of-print 22 April 2022

This editorial refers to 'Effects of aspirin on dementia and cognitive function in diabetic patients: the ASCEND trial', by S. Parish *et al.*, https://doi.org/10.1093/eurheartj/ehac179.

Graphical Abstract



Potential links between heart disease and dementia in patients with diabetes.

EDITORIAL

Is this the end for aspirin in the prevention of dementia in diabetes?

This large well-performed substudy **does not give much hope for aspirin to have a clinically relevant impact on the risk of dementia in patients with diabetes**.

The study confirms the results of the ASPREE (ASPirin in Reducing Events in the Elderly) trial, a randomized trial including 19,114 participants (In The U.S. and Australia) followed over a median of 4.7 years, which **found no evidence that aspirin was effective in reducing risk of dementia**, mild cognitive impairment, or cognitive decline, while being associated with a small increased risk of major bleeding (3.8% vs. 2.8%).

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Circulation

Circulation. 2022;145:648-658.

ORIGINAL RESEARCH ARTICLE

Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis: The AVATAR Trial

Marko Banovic, MD, PhD; Svetozar Putnik, MD, PhD; Martin Penicka, MD, PhD; Gheorghe Doros, PhD; Marek A. Deja, MD, PhD; Radka Kockova, MD, PhD; Martin Kotrc, MD; Sigita Glaveckaite, MD, PhD; Hrvoje Gasparovic, MD, PhD; Nikola Pavlovic, MD, PhD; Lazar Velicki, MD, PhD; Stefano Salizzoni, MD, PhD; Wojtek Wojakowski, MD, PhD; Guy Van Camp, MD, PhD; Serge D. Nikolic, PhD; Bernard Iung, MD; Jozef Bartunek, MD, PhD; on behalf of the AVATAR Trial Investigators*

BACKGROUND: Surgical aortic valve replacement (SAVR) represents a class I indication in symptomatic patients with severe aortic stenosis (AS). However, indications for early SAVR in asymptomatic patients with severe AS and normal left ventricular function remain debated.

METHODS:

The AVATAR trial (Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis) is an investigator-initiated **international prospective randomized controlled trial** that **evaluated the safety and efficacy of early SAVR in the treatment of asymptomatic patients with severe AS**, according to common criteria (valve area ≤1 cm2 with aortic jet velocity >4 m/s or a mean transaortic gradient ≥40 mm Hg), and with normal left ventricular function.

PRIMARY ENDPOINT:

The primary end point was a composite of all-cause mortality or major adverse cardiovascular events (MACEs) composed of acute myocardial infarction, stroke, and unplanned HF hospitalization needing intravenous treatment with diuretics or inotropes.

RESULTS:

Between June 2015 and September 2020, 157 patients (mean age, 67 years; 57% men) were randomly allocated to **early surgery (n=78) or conservative treatment (n=79).**

Follow-up completed in May 2021. **Median follow =32 months;**

Total of 39 events, 13 in early surgery and 26 in the conservative treatment group.

In the early surgery group, 72 patients (92.3%) underwent SAVR with operative mortality of 1.4%. In an intention-to-treat analysis, **patients randomized to early surgery had a significantly lower incidence of primary composite end point** than those in the conservative arm (hazard ratio, 0.46).

No statistical difference in secondary end points, including all-cause mortality, first heart failure hospitalizations, major bleeding, or thromboembolic complications, but trends were consistent with the primary outcome.

CONCLUSIONS:

In **asymptomatic patients with severe AS, early surgery reduced a primary composite** of all-cause death, acute myocardial infarction, stroke, or unplanned hospitalization for heart failure compared with conservative treatment.

This randomized trial provides **preliminary support for early SAVR once AS becomes severe, regardless of symptoms**.

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ARTICLES
https://doi.org/10.1038/s41591-021-01659-1

nature medicine

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OPEN

The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial

Nature Medicine. 2022; Vol 238:568-574.

Adriaan A. Voors[1]✉, Christiane E. Angermann[2], John R. Teerlink[3], Sean P. Collins[4], Mikhail Kosiborod[5,6,7,8], Jan Biegus[9], João Pedro Ferreira[10,11], Michael E. Nassif[5,6], Mitchell A. Psotka[12], Jasper Tromp[13], C. Jan Willem Borleffs[14], Changsheng Ma[15], Joseph Comin-Colet[16], Michael Fu[17], Stefan P. Janssens[18], Robert G. Kiss[19], Robert J. Mentz[20,21], Yasushi Sakata[22], Henrik Schirmer[23], Morten Schou[24], P. Christian Schulze[25], Lenka Spinarova[26], Maurizio Volterrani[27], Jerzy K. Wranicz[28], Uwe Zeymer[29], Shelley Zieroth[30], Martina Brueckmann[31,32], Jonathan P. Blatchford[33], Afshin Salsali[34,35] and Piotr Ponikowski[9]

The sodium–glucose cotransporter 2 inhibitor empagliflozin reduces the risk of cardiovascular death or heart failure hospitalization in patients with chronic heart failure, but whether empagliflozin also improves clinical outcomes when initiated in patients who are hospitalized for acute heart failure is unknown. In this double-blind trial (EMPULSE; NCT04157751), 530 patients with a primary diagnosis of acute de novo or decompensated chronic heart failure regardless of left ventricular ejection fraction were randomly assigned to receive empagliflozin 10 mg once daily or placebo. Patients were randomized in-hospital when clinically stable (median time from hospital admission to randomization, 3 days) and were treated for up to 90 days. The primary outcome of the trial was clinical benefit, defined as a hierarchical composite of death from any cause, number of

METHODS

An **international, Multicenter, Randomized, Double-blind, 90-day Superiority Trial** to Evaluate the Effect on Clinical Benefit, Safety and Tolerability of Once Daily Oral **EMPagliflozin** 10 mg Compared to Placebo, **Initiated in Patients Hospitalized for acUte Heart faiLure** (de Novo or Decompensated Chronic HF) Who Have Been Stabilized (**EMPULSE**)

2020—2021

Primary outcome of the trial was clinical benefit, defined as a hierarchical composite of death from any cause, number of heart failure events and time to first heart failure event, or a 5 point or greater difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score at 90 days.

RESULTS

More patients treated with empagliflozin had clinical benefit compared with placebo (stratified win ratio, 1.36), meeting the primary endpoint.

Clinical benefit was observed for both acute de novo and decompensated chronic heart failure and was observed regardless of ejection fraction or the presence or absence of diabetes.

Empagliflozin was well tolerated; serious adverse events were reported in 32.3% and 43.6% of the empagliflozin- and placebo-treated patients, respectively.

CONCLUSION

These findings indicate that initiation of empagliflozin in patients hospitalized for acute heart failure is well tolerated and results in significant clinical benefit in the 90 days after starting treatment.

Int. J. Med. Sci. 2022;19(7):1118-1121.

IVYSPRING INTERNATIONAL PUBLISHER

International Journal of Medical Sciences

2022; 19(7): 1118-1121. doi: 10.7150/ijms.72772

Review

Empagliflozin in the treatment of heart failure and type 2 diabetes mellitus: Evidence from several large clinical trials

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INTRODUCTION

In recent years, many hypoglycemic drugs, such as **sodium-glucose co-transporter-2 inhibitors (SGLT-2is), have emerged in the treatment of HF**. Although the potential benefits and risks of SGLT-2is are unclear, SGLT-2is significantly reduce cardiovascular events, including hospitalization for HF and all-cause hospitalization or death.

Scandinavian register-based cohort study indicated that **SGLT-2i lowers HF risk compared with dipeptidyl peptidase-4 inhibitor**, another glucose-lowering drug. This **benefit from SGLT-2i may contribute to the upregulation of the renin-angiotensin-aldosterone system**.

EMPA-REG OUTCOME

Randomized, double-blind, placebo-controlled trial to assess the effect empagliflozin on cardiovascular events in adults with type 2 diabetes at high cardiovascular risk.
Patients were treated at **590 sites in 42 countries**. Median observation **time = 3.1 yrs**.

Empagliflozin significantly lowered hospitalization for HF, cardiovascular mortality, and all-cause mortality than placebo.

In short, EMPA-REG OUTCOME demonstrated that **empagliflozin reduced hospitalization for HF risk on top of the standard of care in patients with T2DM and established cardiovascular disease**.

The post hoc evaluation showed that the changes in hematocrit and hemoglobin were the most important mediators of the reduction in hospitalization for HF and death from HF.

EMPRISE

EMPRISE used **real-world data from three databases in the USA** to evaluate the effectiveness, safety, and impact on healthcare utilization of empagliflozin.

Evaluated the impact of empagliflozin on hospitalization for HF and **compared it with sitagliptin, a dipeptidyl peptidase-4 inhibitor, which has proven to have a neutral impact on hospitalization for HF**.

Among included patients, only approximately 5% had existing HF.
Over a **mean follow-up of 5.3 months**, the i**nitiation of empagliflozin decreased hospitalization for HF compared with the initiation of sitagliptin**.
Moreover, some patients with no history of HF developed HF during the follow-up, and **empagliflozin reduced hospitalization for HF regardless of the history of HF**.

EMPERORReduced

An **international, Multicenter, Phase III Randomized, Double-blind Trial** to Evaluate Efficacy and Safety of Once Daily **Empagliflozin** 10 mg Compared to Placebo, **in Patients With Chronic Heart Failure With Reduced Ejection Fraction (HFrEF)**

Indicated that **empagliflozin significantly lowered hospitalization for HF and cardiovascular mortality than placebo, with or without T2DM**.

EMPEROR-Preserved

An **international, Multicenter, A Phase III Randomized, Double-blind Trial** to Evaluate Efficacy and Safety of Once Daily **Empagliflozin** 10 mg Compared to Placebo, **in Patients With Chronic Heart Failure With Preserved Ejection Fraction (HFpEF)**

Indicated that **empagliflozin reduced hospitalization for HF and cardiovascular mortality**.

EMPA-TROPISM

Single U.S. site, double-blind, randomized placebo-controlled trial to determine whether empagliflozin improves cardiac function, exercise performance, and QoL in nondiabetic HFrEF

Empagliflozin was associated with a significant

- **reduction of LV end-diastolic volume and LV end-systolic volume**
- **reductions in LV mass**
- **improvements in LV ejection fraction**
- **improvements in peak O2 consumption**
- **oxygen uptake efficiency slope**
- **6-min walk test**
- **quality of life (Kansas City Cardiomyopathy Questionnaire)**

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Clinical Review & Education

JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Vitamin, Mineral, and Multivitamin Supplementation to Prevent Cardiovascular Disease and Cancer

US Preventive Services Task Force Recommendation Statement

JAMA. 2022;327(23):2326-2333.

US Preventive Services Task Force

IMPORTANCE According to National Health and Nutrition Examination Survey data, 52% of surveyed US adults reported using at least 1 dietary supplement in the prior 30 days and 31% reported using a multivitamin-mineral supplement. The most commonly cited reason for using supplements is for overall health and wellness and to fill nutrient gaps in the diet. Cardiovascular disease and cancer are the 2 leading causes of death and combined account for approximately half of all deaths in the US annually. Inflammation and oxidative stress have been shown to have a role in both cardiovascular disease and cancer, and dietary supplements may have anti-inflammatory and antioxidative effects.

Editorial page 2

Multimedia

Related article p
and JAMA Patie
page 2364

Supplemental c

Related article a
jamainternalme

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

REFERENCE: https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/grade-definitions

Summary of Recommendation

Community-dwelling, nonpregnant adults	The USPSTF recommends against the use of beta carotene or vitamin E supplements for the prevention of cardiovascular disease or cancer.	D
Community-dwelling, nonpregnant adults	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the use of multivitamin supplements for the prevention of cardiovascular disease or cancer. See the Practice Considerations section for additional information regarding the I statement.	I
Community-dwelling, nonpregnant adults	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the use of single- or paired-nutrient supplements (other than beta carotene and vitamin E) for the prevention of cardiovascular disease or cancer. See the Practice Considerations section for additional information regarding the I statement.	I

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Research

JAMA Int Med. 2022;182(8):840-848.

JAMA Internal Medicine | Original Investigation

Association of the "Weekend Warrior" and Other Leisure-time Physical Activity Patterns With All-Cause and Cause-Specific Mortality
A Nationwide Cohort Study

Mauricio dos Santos, MSc; Gerson Ferrari, PhD; Dong Hoon Lee, ScD; Juan Pablo Rey-López, PhD; Dagfinn Aune; Bing Liao, MSc; Wentao Huang, MSc; Jing Nie, BSc; Yafeng Wang, PhD; Edward Giovannucci, MD, ScD; Leandro F. M. Rezende, ScD

IMPORTANCE It is unclear whether the weekly recommended amount of moderate to vigorous physical activity (MVPA) has the same benefits for mortality risk when activity sessions are spread throughout the week vs concentrated in fewer days.

OBJECTIVE To examine the association of weekend warrior and other patterns of leisure-time physical activity with all-cause and cause-specific mortality.

DESIGN, SETTING, AND PARTICIPANTS This large nationwide prospective cohort study included 350 978 adults who self-reported physical activity to the US National Health Interview Survey from 1997 to 2013. Participant data were linked to the National Death Index through December 31, 2015.

Supplemental content

IMPORTANCE

It is unclear whether the weekly recommended amount of moderate to vigorous physical activity (MVPA) has the same benefits for mortality risk when **activity sessions are spread throughout the week vs concentrated in fewer days**.

DESIGN, SETTING, AND PARTICIPANTS

Large **nationwide prospective cohort study**

350 978 adults who self-reported physical activity to the US National Health Interview Survey from 1997 to 2013.

EXPOSURES

Participants were grouped by self-reported activity level:

physically inactive (<150 minutes per week [min/wk] of MVPA) or physically active (≥150 min/wk of moderate OR ≥75 min/wk of vigorous activity)

The active group was further classified by pattern:

weekend warrior (1-2 sessions/wk) or regularly active (≥3 session/wk); and then, by frequency, duration / session, and intensity of activity.

MAIN OUTCOMES AND MEASURES

All-cause, cardiovascular disease (CVD), and cancer mortality.

Statistical analyses were performed in April 2022

RESULTS

Total of 350 978 participants

mean age, 41.4 years;

192,432 [50.8%] women;

209,432 [67.8%] Non-Hispanic White;

21 898 deaths, including 4130 from CVD and 6034 from cancer.

median follow-up of 10 years,

Compared with inactive people, both regularly active people and “weekend warriors” had lower risks for all-cause, cardiovascular-related, and cancer-related death, after adjustment for numerous variables; however, only the results for regularly active people were statistically significant.

After adjustment for total amount of moderate-to-vigorous activity, regularly active people and “weekend warriors” had similar all-cause, cardiovascular-related, and cancer-related mortality.

CONCLUSIONS AND RELEVANCE

Individuals who engage in active patterns of physical activity, whether weekend warrior or regularly active, experience lower all-cause and cause-specific mortality rates than inactive individuals.

Significant differences were not observed for all-cause or cause-specific mortality between weekend warriors and regularly active participants after accounting for total amount of MVPA; **therefore, individuals who engage in the recommended levels of physical activity may experience the same benefit whether the sessions are performed throughout the week or concentrated into fewer days.**

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BACKGROUND

The International Consensus Meeting (ICM) – Venous Thromboembolism (VTE):

Delegates from 135 international societies, 68 countries, and various specialties, including anesthesia, cardiology, hematology, internal medicine, and orthopedics, **analyzed the literature in a systematic review format and created practical recommendations** related to all subspecialities in orthopedics with global applications.

This immense initiative engaged nearly 600 experts who followed the strict Delphi process, to generate the document over a period of 1 year, and with the critical guidance of the steering committee and engagement of the organizing committee, librarians, biostatisticians, epidemiologists, and experts from the Cochrane group.

ALL published work related to VTE and orthopedics was reviewed to generate a response/ recommendation to the nearly 200 issues (questions) that had been collated from the field.

J Bone Joint Surg Am. 2022;104 Suppl 1:180-231

Recommendations from the ICM-VTE: Hip & Knee

The ICM-VTE Hip & Knee Delegates*

3 - What is the most optimal VTE prophylaxis following TKA/THA?

Response/Recommendation: Low-dose aspirin (ASA) is currently the most effective and safest method of prophylaxis against venous thromboembolism (VTE) in patients undergoing total joint arthroplasty (TJA). We recommend the use of low-dose ASA as the primary method of VTE prophylaxis in all patients undergoing TJA, including moderate-to high-risk patients.

Strength of Recommendation: Strong.

Delegates vote: Agree 76.92% Disagree 19.66% Abstain 3.42% (Strong Consensus).

Research

JAMA | Original Investigation

Effect of Aspirin vs Enoxaparin on Symptomatic Venous Thromboembolism in Patients Undergoing Hip or Knee Arthroplasty
The CRISTAL Randomized Trial

JAMA. 2022;328(8):719-727.

CRISTAL Study Group

IMPORTANCE There remains a lack of randomized trials investigating aspirin monotherapy for symptomatic venous thromboembolism (VTE) prophylaxis following total hip arthroplasty (THA) or total knee arthroplasty (TKA).

OBJECTIVE To determine whether aspirin was noninferior to enoxaparin in preventing symptomatic VTE after THA or TKA.

DESIGN, SETTING, AND PARTICIPANTS Cluster-randomized, crossover, registry-nested trial across 31 hospitals in Australia. Clusters were hospitals performing greater than 250 THA or TKA procedures annually. Patients (aged ≥18 years) undergoing hip or knee arthroplasty procedures

Visual Abstract

Editorial page 712

Supplemental content

OBJECTIVE To **determine whether aspirin was noninferior to enoxaparin in preventing symptomatic VTE after THA or TKA**.

DESIGN, SETTING, AND PARTICIPANTS

Cluster-randomized, crossover, registry-nested trial across 31 hospitals in Australia.

Clusters were hospitals performing greater than 250 THA or TKA procedures annually. Patients (age≥18 years) undergoing hip or knee arthroplasty procedures were enrolled. 9711 eligible patients (5675 in the aspirin group and 4036 in the enoxaparin group).

Median age 67 yrs (aspirin) and 68 years (enoxaparin); more females in both

INTERVENTIONS

Hospitals were randomized to administer aspirin (100mg/d) or enoxaparin (40mg/d) for 35 days after THA and for 14 days after TKA.

MAIN OUTCOMES AND MEASURES

The primary outcome was symptomatic VTE within 90 days, including pulmonary embolism and deep venous thrombosis (DVT) (above or below the knee). The noninferiority margin was 1%.

RESULTS

9203 patients completed the trial.

Within 90 days of surgery, symptomatic VTE occurred in 256 patients, including pulmonary embolism (79 cases), above-knee DVT (18 cases), and below-knee DVT (174 cases).

The symptomatic VTE rate in the aspirin group was 3.45% and in the enoxaparin group was 1.82%. This failed to meet the criterion for noninferiority for aspirin and was significantly superior for enoxaparin.

CONCLUSIONS AND RELEVANCE

Among patients undergoing hip or knee arthroplasty for osteoarthritis, aspirin compared with enoxaparin resulted in a significantly higher rate of symptomatic VTE within 90 days, defined as below- or above-knee DVT or pulmonary embolism.

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Recommendations from the ICM-VTE: Hip & Knee

The ICM-VTE Hip & Knee Delegates*

Effect of Aspirin vs Enoxaparin on Symptomatic Venous Thromboembolism in Patients Undergoing Hip or Knee Arthroplasty
The CRISTAL Randomized Trial

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BACKGROUND

ACTIV-6, an ongoing, decentralized, double-blind, randomized, placebo-controlled platform trial, was designed to evaluate repurposed therapies in outpatients with mild to moderate COVID-19.

2021—2023 (94 study locations in the U.S.)

- Ivermectin 300-400 µg/kg, daily for 3 days
- Fluvoxamine 50 mg twice a day for 10 day
- Fluticasone inhaled 200 µg (1 blister) once daily for 14 days
- Ivermectin 400 -600 µg/kg, daily for 6 days
- Fluvoxamine 50 mg twice a day for 1 day, followed by 100 mg twice a day for 12 days
- Montelukast 10 mg once a day for 14 days
- Placebo

Research

JAMA | Original Investigation

JAMA. 2022;328(16):1595-1603.

Effect of Ivermectin vs Placebo on Time to Sustained Recovery in Outpatients With Mild to Moderate COVID-19
A Randomized Clinical Trial

Susanna Naggie, MD, MHS; David R. Boulware, MD, MPH; Christopher J. Lindsell, PhD; Thomas G. Stewart, PhD; Nina Gentile, MD; Sean Collins, MD, MSci; Matthew William McCarthy, MD; Dushyantha Jayaweera, MD; Mario Castro, MD, MPH; Mark Sulkowski, MD; Kathleen McTigue, MD, MPH, MS; Florence Thicklin; G. Michael Felker, MD, MHS; Adit A. Ginde, MD, MPH; Carolyn T. Bramante, MD, MPH; Alex J. Slandzicki, MD; Ahab Gabriel, MD; Nirav S. Shah, MD, MPH; Leslie A. Lenert, MD, MS; Sarah E. Dunsmore, PhD; Stacey J. Adam, PhD; Allison DeLong, BS; George Hanna, MD; April Remaly, BA; Rhonda Wilder, MS; Sybil Wilson, RN; Elizabeth Shenkman, PhD; Adrian F. Hernandez, MD, MHS; for the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV-6) Study Group and Investigators

IMPORTANCE The effectiveness of ivermectin to shorten symptom duration or prevent hospitalization among outpatients in the US with mild to moderate symptomatic COVID-19 is unknown.

Visual Abstract

Supplemental co

OBJECTIVE

To **evaluate the efficacy of ivermectin, 400 µg/kg, daily for 3 days** compared with placebo for the treatment of early mild to moderate COVID-19.

DESIGN, SETTING, AND PARTICIPANTS

ACTIV-6

A total of **1591 participants aged 30 years and older with confirmed COVID-19,** experiencing 2 or more symptoms of acute infection for 7 days or less, were enrolled from June 23, 2021, through February 4, 2022, with follow-up data through May 31, 2022, at 93 sites in the US.

INTERVENTIONS

Participants were randomized to receive ivermectin, 400 µg/kg (n = 817), daily for 3 days or placebo (n = 774).

MAIN OUTCOMES AND MEASURES

Time to sustained recovery, defined as at least 3 consecutive days without symptoms.

7 secondary outcomes, including a composite of hospitalization or death by day 28.

RESULTS

1800 participants who were randomized (mean age, 48 years; 932 women [58.6%]; 753 [47.3%] reported receiving at least 2 doses of a SARS-CoV-2 vaccine).

1591 completed the trial.

Posterior probability = prior probability + new evidence (called likelihood)

The posterior probability of improvement in time to recovery in those treated with ivermectin vs placebo had a hazard ratio of 1.07, with a posterior probability of benefit of .91. This **did not meet the prespecified threshold of posterior probability** greater than .95. No significant differences in secondary outcomes too.

CONCLUSIONS AND RELEVANCE

Among outpatients with mild to moderate COVID-19, **treatment with ivermectin**, compared with placebo, **did not significantly improve time to recovery**.

These findings do not support the use of ivermectin in patients with mild to moderate COVID-19.

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DOI: 10.1111/jgs.17913

Journal of the
American Geriatrics Society

JAGS. 2022;70(10):2847–2857.

End-of-life healthcare utilization and palliative care use among older adults with limited English proficiency

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Abstract

Background: Little is known about end-of-life healthcare utilization and palliative care use among older adults with serious illness and limited English proficiency (LEP).

METHODS:

retrospective analysis of seriously-ill older adults (65+) with and without LEP, from a large health system, who died between 2010 and 2018.

RESULTS:

Among 18,490 decedents, 1363 had LEP.

Patients with LEP were more likely to be

- **older at time of death (median age 80 vs 77 years),**
- **female (48% vs 44%),**
- **of Asian descent (64% vs 4%),**
- **of Hispanic ethnicity (10% vs 2%),**
- **with <12th grade education (38% vs 9%),**
- **With Medicaid (36% vs 6%).**

In the last 30 days of life, patients with LEP had higher odds of

- ED visits,
- readmission
- in-hospital death

Findings were similar in the last 180-days of life.

Only 14% of patients with LEP and 10% of those without LEP received palliative care consultation in the last month of life.

Patients with LEP were less likely to have advance care planning documents than patients without LEP.

CONCLUSIONS:

Older adults with serious illness and LEP have higher rates of end-of-life healthcare utilization.

Additional research is needed to identify drivers of these differences and **inform linguistically- and culturally-appropriate interventions** to improve end-of-life care in this population.

Received: 5 January 2022 | Revised: 27 May 2022 | Accepted: 9 June 2022

DOI: 10.1111/jgs.17952

Journal of the
American Geriatrics Society

JAGS. 2022;70(10):2871–2883.

Associations between dementia diagnosis and end-of-life care utilization

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Abstract

Background: Dementia is a leading cause of death for older adults and is more common among persons from racial/ethnic minoritized groups, who also tend to experience more intensive end-of-life care. This retrospective cohort

METHODS:

Analysis of administrative claims data for 463,590 Medicare fee-for-service decedents (2016 to 2018)

RESULTS:

- 54% female; 51% had a dementia diagnosis claim
- 85% non-Hispanic White, 8% non-Hispanic Black, and 4% Hispanic

Decedents with dementia had lower odds of receiving intensive services (hospital death, hospitalization)

Decedents with dementia had higher odds of receiving timely hospice care.

Compared to non-Hispanic White individuals, **persons from racial/ethnic minoritized groups were more likely to receive intensive services.**

This effect was more pronounced among persons with dementia.

CONCLUSIONS:

Although overall dementia was associated with fewer intensive services near death, **beneficiaries from racial/ethnic groups minoritized with dementia experienced more intensive service use.**

Particular attention is needed to ensure care aligns with the needs and preferences of persons with dementia and from racial/ethnic minoritized groups.

Received: 28 January 2022 | Revised: 5 May 2022 | Accepted: 9 May 2022

DOI: 10.1111/jgs.17912

Journal of the
American Geriatrics Society

JAGS. 2022;70(10):2858–2870.

A national study of disenrollment from hospice among people with dementia

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[1]Department of Physiological Nursing, University of California, San Francisco, California, USA

Abstract

Background: People with dementia (PWD) are at high risk for hospice disen-

DESIGN:

Retrospective, observational cohort study of 100% Medicare beneficiaries with dementia aged 65 and older enrolled in the Medicare Hospice Benefit between July 2012 and December 2017.

RESULTS:

Among 867,695 hospice enrollees with dementia, (within 1-year of their index admission) 70,945 (8.2%) were disenrolled due to extended prognosis and 43,133 (5.0%) revoked.

RESULTS (cont'd):

There was **substantial variation in hospice provider disenrollment** due to extended prognosis and revocation.

Among hospital referral regions (HRR), there was **more variation in revocation** than extended prognosis, with much **higher revocation rates noted in HRRs located in the Southeast and Southern California**.

A number of patient and hospice characteristics were associated with higher odds of both types of disenrollment (younger age, female sex, minoritized race and ethnicity, Medicaid dual eligibility, Medicare Part C enrollment), while some were associated with revocation only (more comorbidities, newer, smaller, and for-profit hospices).

CONCLUSIONS:

In this nationally representative study of hospice enrollees with dementia, **hospice disenrollment varied by type of hospice, geographic region, and patient characteristics including age, sex, race, and ethnicity**.

These findings **raise important questions about whether and how the Medicare Hospice Benefit could be adapted** to reduce disparities and better support PWD.

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DOI: 10.1111/jgs.17771

Journal of the
American Geriatrics Society

JAGS. 2022;70(7):2008–2018.

Sliding scale insulin use in a national cohort study of nursing home residents with type 2 diabetes

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Abstract

Background: Guidelines discourage sliding scale insulin (SSI) use after the first week of a nursing home (NH) admission. We sought to determine the prevalence of SSI and identify factors associated with stopping SSI or transitioning to another short-acting insulin regimen.

BACKGROUND:

Guidelines discourage sliding scale insulin (SSI) use after the first week of a nursing home (NH) admission.

Researchers sought to **determine the prevalence of SSI and identify factors associated with stopping SSI or transitioning to another short-acting insulin regimen**.

METHODS:

Observational study from 2013 to 2017 of non-hospice **Veterans Affairs NH residents with type 2 diabetes** and a NH admission over 1 week

Compared the weekly prevalence of SSI versus two other short-acting insulin regimens – fixed dose insulin (FDI) or correction dose insulin (CDI, defined as variable SSI given alongside fixed doses of insulin) – from week 2 to week 12 of admission.

Among those on SSI in week 2, researchers. **examined factors associated with stopping SSI or transitioning to other regimens by week 5**

Factors included

- demographics (e.g., age, sex, race/ethnicity),
- frailty-related factors (e.g., comorbidities, cognitive impairment, functional impairment), and
- diabetes-related factors (e.g., HbA1c, long-acting insulin use, hyperglycemia, and hypoglycemia).

RESULTS:

In week 2, 21% of the cohort was on SSI, 8% was on FDI, and 7% was on CDI.

SSI was the most common regimen in frail subgroups (with moderate–severe cognitive impairment).

SSI prevalence decreased steadily from 21% to 16% at week 12, mostly through stopping SSI.

Diabetes-related factors (e.g., hyperglycemia) were more strongly associated with continuing SSI or transitioning to a non-SSI short-acting insulin regimen than frailty related factors.

CONCLUSIONS:

SSI is the most common method of administering short-acting insulin in NH residents.

More research needs to be done to explore why sliding scale use persists weeks after NH admission and explore how this practice can be replaced with safer, more effective, and less burdensome regimens.

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Glycemic treatment deintensification practices in nursing home residents with type 2 diabetes

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Abstract

Background: Older nursing home (NH) residents with glycemic over-treatment are at significant risk of hypoglycemia and other harms and may benefit from deintensification. However, little is known about deintensification practices in this setting.

BACKGROUND:

Older nursing home (NH) residents with glycemic overtreatment are at significant risk of hypoglycemia and other harms and may benefit from deintensification.

METHODS:

Cohort study from 2013 to 2017 among **Veterans Affairs NH residents age ≥ 65 with type 2 diabetes** and a NH length of stay (LOS) ≥ 30 days and an HbA1c result during their NH stay.

Defined overtreatment as HbA1c <6.5 with any insulin use, and
potential overtreatment as HbA1c <7.5 with any insulin use or
HbA1c <6.5 on any glucose-lowering medication (GLM) other than metformin alone.

Primary outcome was continued glycemic overtreatment without deintensification 14 days after HbA1c.

RESULTS:

Of the 7422 included residents,

- 17% of residents met criteria for overtreatment and
- an additional 23% met criteria for potential overtreatment

Among residents overtreated and potentially overtreated at baseline,
27% and 19%, respectively had medication regimens deintensified
(73% and 81%, respectively, continued to be overtreated).

Long-acting insulin use and hyperglycemia ≥300 mg/dL before index HbA1c were associated with increased odds of continued overtreatment.

Severe functional impairment (MDS-ADL score ≥ 19) was associated with decreased odds of continued overtreatment.

Hypoglycemia was NOT associated with decreased odds of overtreatment.

CONCLUSIONS:

Overtreatment of diabetes in NH residents is common and only a minority of residents have their medication regimens appropriately deintensified.

Many NH residents who are unlikely to benefit from tight glycemic control and are at high risk of hypoglycemia continue to receive insulin and other medications that increase hypoglycemia risk even after HbA1c results suggest overtreatment.

In addition to hypoglycemia risk, factors such as cognitive and functional impairment should be considered when identifying patients for treatment deintensification.

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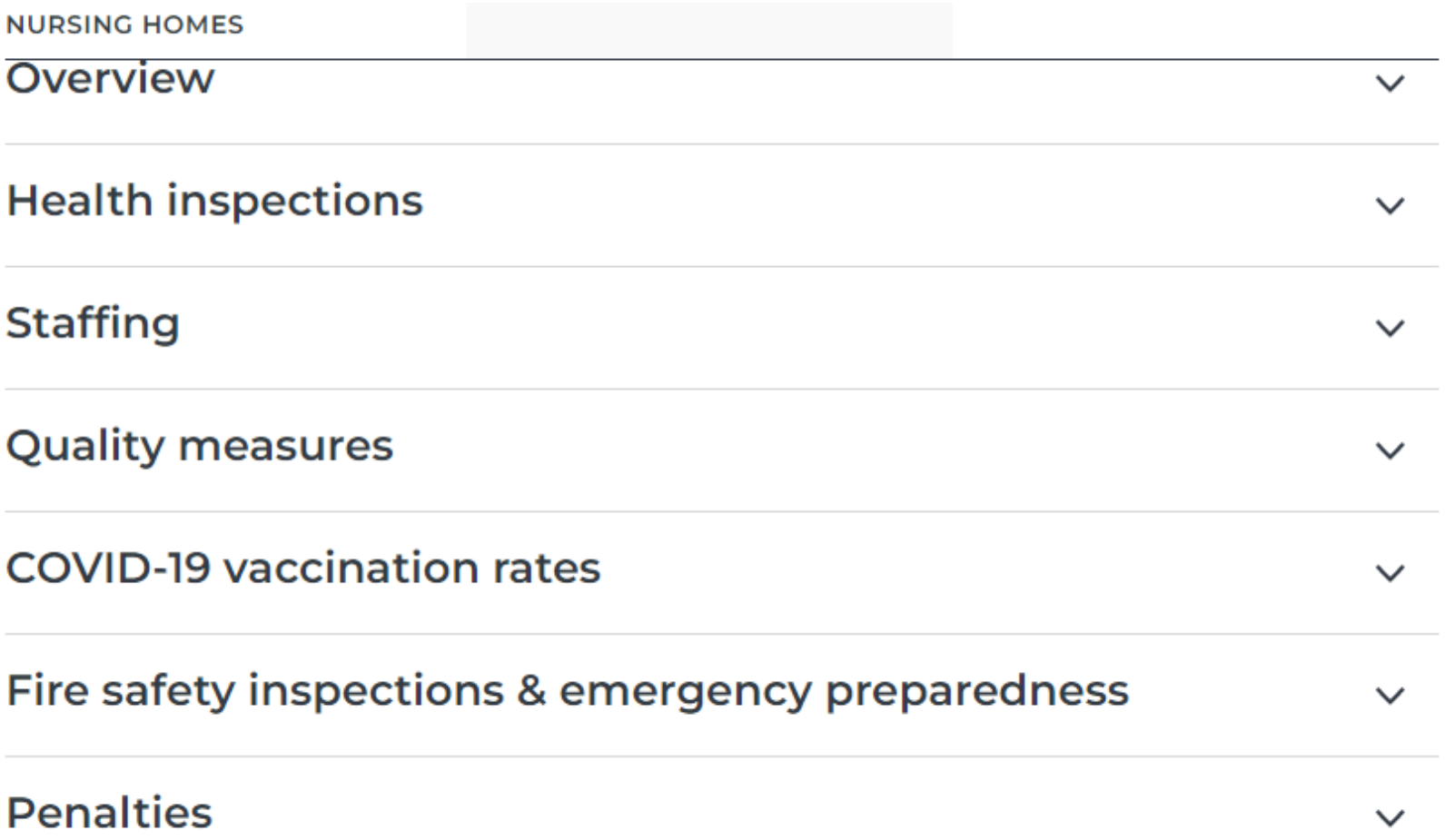
Nursing Home Care Compare web site

CMS created the **Five-Star Quality Rating System** to help consumers, their families, and caregivers compare nursing homes more easily and to help identify areas about which you may want to ask questions.



https://www.medicare.gov/care-compare/?providerType=NursingHome&redirect=true

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CLINICAL INVESTIGATIONS

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Association between staff turnover and nursing home quality – evidence from payroll-based journal data

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Abstract

Background: Staff turnover is considered an important indicator of nursing home quality. We used auditable staffing data from the Centers for Medicare & Medicaid Services (CMS) Payroll-Based Journal (PBJ) system to calculate turnover measures for nurse staff and administrators and examined the relationship between turnover and nursing home quality.

BACKGROUND:
Staff turnover is considered an important indicator of nursing home quality.

METHODS:
Used auditable staffing data from the Centers for Medicare & Medicaid Services (CMS) Payroll-Based Journal (PBJ) system to calculate turnover measures for nurse staff and administrators and examined the relationship between turnover and nursing home quality.

Included data from 13,631 nursing homes
Identified turnover based on gaps in days worked by eligible employees

Linked staff turnover measures to nursing home quality measures and star ratings published on CMS' Care Compare website in January 2020 and examined the relationship between turnover and quality of care.

RESULTS:

Mean annual turnover rates were about 44% for RNs and 46% for total nurse staff.

On average, there was one administrator leaving each nursing home during this period although about half of nursing homes had no administrator turnover.

Turnover rates varied greatly across nursing homes.

For-profit and larger nursing homes had higher turnover rates.
Higher turnover was consistently associated with lower quality of care.

CONCLUSIONS:

This study highlights the importance of staff turnover due to its relationship to nursing home quality.

In January 2022, CMS started posting turnover measures on Care Compare to allow consumers to use this information in their assessment of nursing home quality and to motivate nursing homes to implement innovative strategies to retain staff.

While these actions are challenging, they are nonetheless warranted for improving the quality of care for nursing home residents.

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VIEWPOINT

Moving to More Evidence-Based Primary Care Encounters
A Farewell to the Review of Systems

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In the practice of medicine, what is documented in a patient's medical record helps ensure continuity of care, facilitate coordination between clinicians, support quality improvement and research, can be useful in medical-legal disputes, and, increasingly, makes medical care more transparent to patients. However, over the years, documentation has been increasingly driven by billing and coding requirements. One example is the review of systems (ROS). For decades, clinicians were reimbursed at a higher level by the Centers for Medicare & Medicaid Services (CMS) if visits included an ROS. For example, billing for a "comprehensive" visit was allowed if, among other required components, a "complete ROS" with inquiries about symptoms from at least 10 of 14 tronic health records created visit templates that prepopulated screening ROS questions with patients' prior responses, introducing the risk of inaccuracy.

On January 1, 2021, previous detailed documentation requirements, including for the ROS, were replaced by CMS with visits reimbursed based on complexity of medical decision-making or total clinician time spent.[2] Other newer payment models, such as capitation, have also been adopted in some health systems, with insurers paying a set amount for each patient annually regardless of number or complexity of visits. Eliminating the tradition-based ROS can be slow. Electronic medical records still contain ROS templates, preserving ineffective practices. In our practice settings, 18 months after the

On January 1, 2021, previous **detailed documentation requirements,** including for the ROS, **were replaced by CMS with visits reimbursed based on complexity of medical decision-making or total clinician time spent.**

SUBTRACT

- Review of Systems (RO) may now be de-adopted.
- Routine physical examinations addressing asymptomatic body parts and organ systems, may also be candidates for de-adoption.

ADD

- Using the USPSTF recommendations as a guide, offer and document services that represent evidence-based care to have the greatest influence on improving health.
  - Apply recommendations with evidence of great or moderate net benefit, (A and B recommendations).
  - Apply recommendations based on risk factors: trigger offers of care and identify stopping points when benefits decrease.
  - Target higher-risk individuals for greater health benefit
  - Do not spend time offering care for which there is no net benefit or greater harm exists (D recommendations).
- Vaccinations
- Behavioral Counseling to Promote a Healthy Lifestyle
- Shared Decision-making

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JAMA. 2022;328(16):1589-1590.

VIEWPOINT

Readmission Reduction as a Hospital Quality Measure
Time to Move on to More Pressing Concerns?

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In a 2009 study, Jencks et al[1] reported that among 11.8 million Medicare beneficiaries who were hospitalized in 2003 to 2004, 19.6% were readmitted in the first month after the hospitalization, and these readmissions accounted for an estimated cost of $41 billion annually. Researchers and policy makers inferred that if a significant proportion of readmissions was caused by failures of the health care system—whether due to inadequate treatment during the initial hospitalization or failure of care coordination after hospital discharge—then the adoption of policies designed to reduce inappropriate readmissions would be warranted, particularly because hospitals receive additional payments when patients are readmitted. These findings contributed to the development of the Hospital Readmissions Reduc-

introduction of HRRP and other ACA programs; other studies were similarly positive, suggesting that HRRP might be reducing 30-day readmissions by as much as 1% annually. Gupta[3] estimated that reductions in readmissions saved Medicare $620 million annually.

However, a growing body of literature now suggests that the reported reductions in readmissions may have been overstated. Wadhera et al[4] found that an increasing number of patients who previously would have been readmitted instead were treated under observation status. Other investigators found that much of the purported reduction in readmissions could be explained by a concurrent change in billing standards that allowed hospitals to submit a larger number of comorbid diagnoses

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Researchers and policy makers inferred that if a significant proportion of readmissions was caused by failures of the health care system – **whether due to inadequate treatment during the initial hospitalization or failure of care coordination after hospital discharge—then the adoption of policies designed to reduce inappropriate readmissions would be warranted**, particularly because hospitals receive additional payments when patients are readmitted.

These findings contributed to the development of the Hospital Readmissions Reduction Program (HRRP), enacted in 2010 as part of the Patient Protection and Affordable Care Act (ACA).

Through the HRRP, in 2012 **most US hospitals became "at risk" for a 0% to 3% reduction** (capped at 1% during the first year) **in Medicare diagnosis related group payments** based on their hospital's excess readmission ratio calculated for 3 specified conditions **(acute myocardial infarction, heart failure, and pneumonia), with chronic obstructive pulmonary disease, coronary artery bypass surgery, and total joint replacement** added later.

The persistent focus on readmissions during the past decade, although undoubtedly leading to some improvements in care, has had minimal demonstrable benefit.

Moreover, the HRRP has distracted clinicians and health system leaders from other crucial quality concerns.
As with many other quality measures, the **HRRP has led to gamesmanship whereby hospitals have taken predictable actions in their coding practices and admission processes and protocols in an effort to minimize the probability of receiving penalties**.

After implementation of the HRPP, initial studies were encouraging. For example, in 2016, Zuckerman et al reported an approximately **4% absolute reduction in 30-day readmissions** after the introduction of HRRP and other ACA programs; **other studies were similarly positive**, suggesting that **HRRP might be reducing 30-day readmissions by as much as 1% annually**. Gupta estimated that **reductions in readmissions saved Medicare $620 million annually**.

VIEWPOINT: Reported reductions in readmissions may have been overstated.

U.S. practices for healthcare coding and billing:

- **Patients who previously would have been readmitted instead were treated under observation status**.

- Concurrent change in billing standards that **allowed hospitals to submit a larger number of comorbid diagnoses when submitting claims, thereby increasing the expected number of readmissions**.

Other unrelated temporal factors:

International comparisons also call into question the effectiveness of HRRP. Longitudinal studies have found that **reductions in readmission rates in the US generally have been matched by reductions in other countries that did not introduce readmission reduction policies**.

Indirect costs of the program

Costs are incurred by hospitals when they devote personnel and resources to myriad interventions designed to reduce readmissions (some of which are likely beneficial for patients), but also **in their efforts to improve coding and documentation that influence calculated observed-to-expected readmission rates through risk adjustment**.

Not all readmissions are preventable

In one study less than 36% of early readmissions (within 7 days of discharge) and 23% of late ones (8--30days after discharge) were preventable.

Identification of other locations of care as targets

In the same study, **hospitals were identified as the ideal location to target these preventable readmissions in less than half (47%) of early readmissions and 26% of late readmissions**. **Alternatively**, **the patient's home** was identified as the ideal target in 14% of early readmissions and 19% of late ones; **outpatient clinic**, in 7% and 15%, respectively; and **emergency department**, in 4% for both.

Recognition of the **contribution of disadvantage and adverse social determinants of health in driving hospital readmissions** at both the individual and hospital level.

SUGGESTIONS

Readmissions should continue to be measured and tracked, but the **financial penalties associated with HRRP could be withdrawn**.

ADDITIONAL SUGGESTIONS: The 2013 Agency for Healthcare Research and Quality expert panel **identified an array of patient safety practices with significantly stronger evidence-based support than readmissions**.

- preoperative surgical and anesthesia checklists,
- clinical bundles and order sets to prevent catheter-associated infections, and
- expanded use of clinical pharmacists to reduce adverse drug events

Other measures: reallocate resources toward treatments supported by extremely strong bodies of evidence, currently underused, and under the direct control of hospitals OR other opportunities for improvement:

- improving use of evidence based therapies for patients hospitalized with CHF
- reperfusion therapy for patients with acute stroke
- clinician and hospital personnel wellness
- patient experience
- addiction treatment services
- palliative care

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VIEWPOINT

Social Media and Medical Misinformation
Confronting New Variants of an Old Problem

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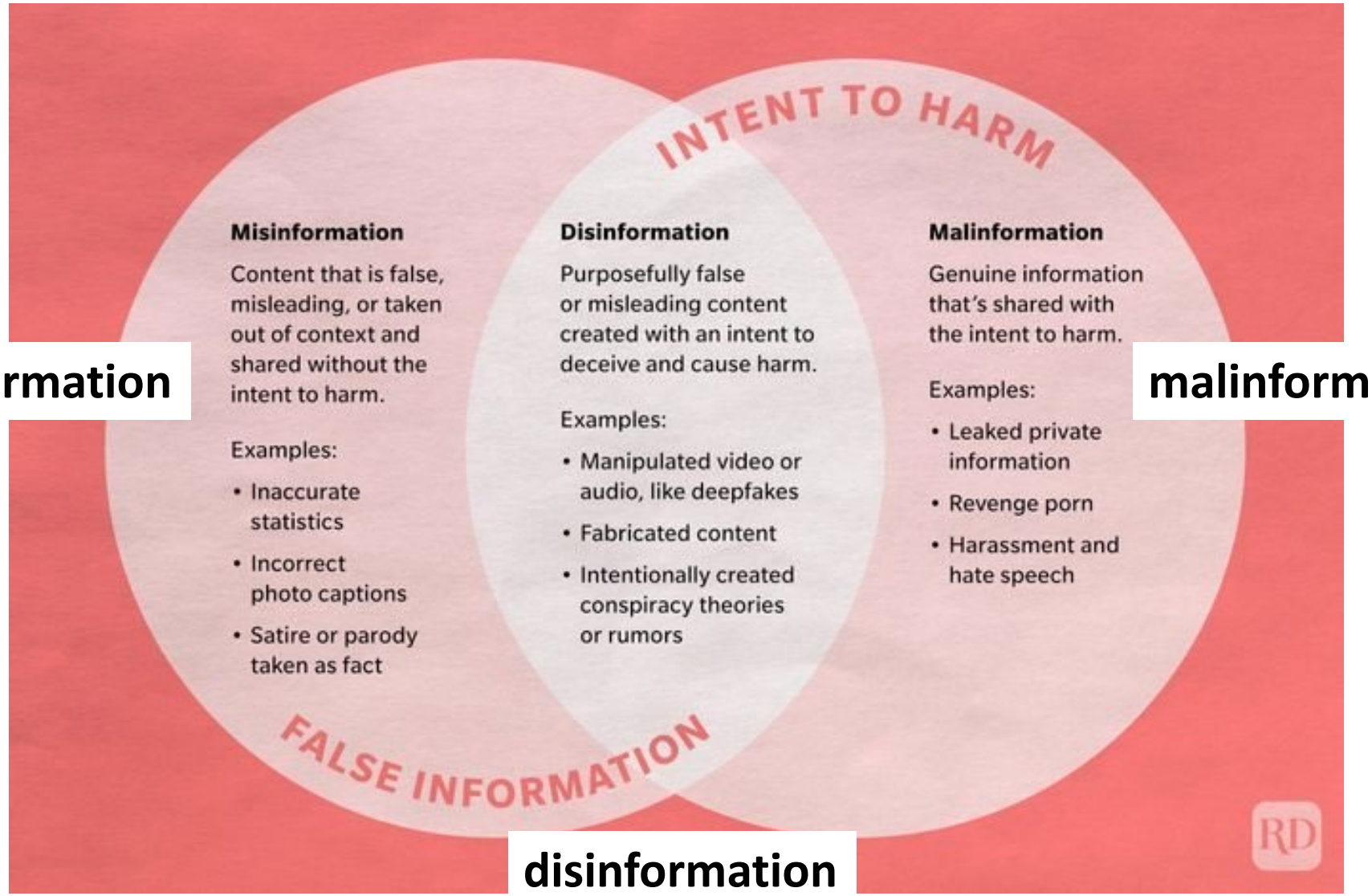
The spread of false and misleading health information has increased substantially in recent years. During the COVID-19 pandemic, for example, misinformation contributed to the use of unproven treatments, nonadherence to mitigation measures, and high levels of vaccine hesitancy. A study based on counterfactual simulation modeling suggested that higher immunization rates could have prevented nearly half of COVID-19–related deaths in the US between January 1, 2021, and April 30, 2022.[1]

Many factors have contributed to the spread of medical misinformation and to a broader degradation of the epistemic environment: declining trust in institutions, splintering of the media ecosystem, deepen-

individuals can dominate a conversation: according to a 2021 analysis, only 12 accounts, known as the "disinformation dozen," were responsible for 65% of antivaccine information on Twitter, Facebook, and Instagram.[4] Disinformation is a subset of misinformation that is deliberately deceptive and is usually organized and designed to advance a specific agenda. Efforts to curtail misinformation and disinformation are often met with concerns about restricting free speech, alleged to be violating if not the letter of the First Amendment, then its spirit. As private entities, social media platforms have wide latitude to enforce terms of use policies.

What can be done? The ABIM Foundation dedi-

misinformation



malinformation

disinformation

https://www.rd.com/article/misinformation-vs-disinformation/

Social media platforms are sometimes referred to as the new town square, online spaces where people can connect with one another, share their views, and debate issues of importance.

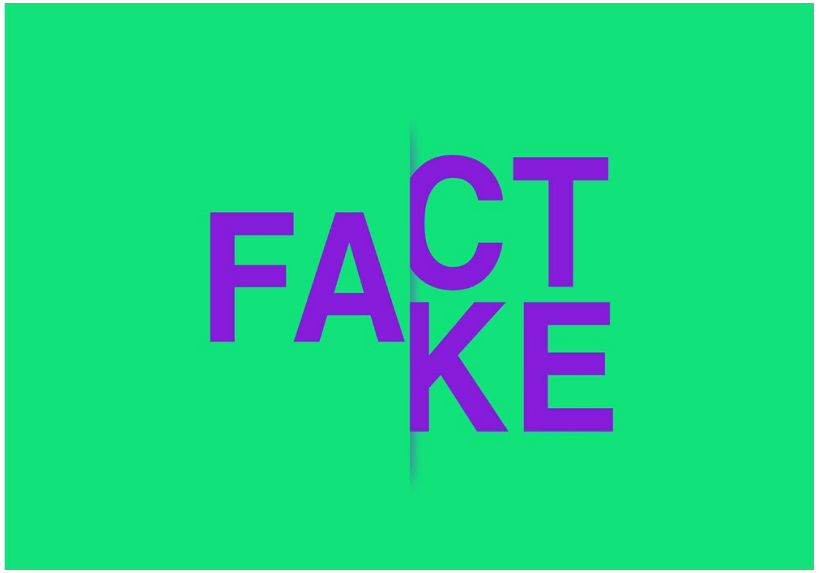
In many respects, however, **individuals can dominate a conversation**: according to a 2021 analysis, **only 12 accounts, known as the "disinformation dozen," were responsible for 65% of antivaccine information on Twitter, Facebook, and Instagram**.

WHAT CAN BE DONE?

The ABIM Foundation dedicated its 2022 Forum to identifying paths toward mitigating the harmful effects of misinformation. Several
themes and proposals emerged, including

- **algorithmic adjustment**
- **misinformation research and surveillance**
- **medical professional training**
- **community engagement**
- **self regulation of the medical profession**

- **algorithmic adjustment**
  redesigning algorithms to reduce the visibility of misinformation and elevate high-quality information (for example, National Academy of Medicine partnered with YouTube)
- **misinformation research and surveillance**
  (for example, exposing individuals to cross-attitudinal news outlets and prompting them to think about accuracy; create a comprehensive research agenda for the development of a misinformation surveillance and response system)
- **medical professional training**
  (for example, educate clinicians on how to address medical misinformation - emphasize proactive engagement, empathic listening, and elicitation of patients' values, concerns, and lived experiences)
- **community engagement**
  (for example, virtual town halls with patients and families)
- **self regulation of the medical profession**
  (Federation of State Medical Boards issued a statement declaring that physicians who knowingly spread demonstrably false information risk suspension or revocation of their medical licenses, and several boards, including the American Board of Internal Medicine, have supported this position.



NOW THAT YOU KNOW WHAT CAN BE DONE AND/OR IS BEING DONE,

WHAT WILL YOU DO ABOUT IT?

THANK YOU for LISTENING!