

Knowledge Gaps and Issues in Clinical Trials of Medications for Older Adults

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Randomized Controlled Drug Trials

- Purpose: To determine efficacy
 - *Is this drug beneficial, and do the benefits outweigh the risks?*
- Population: Homogeneous
 - Groups differ only by study drug exposure
 - Restrictive Inclusion/exclusion criteria
 - Age criteria
- If statistically significant difference found, there may be no further or longer trials done

Resulting in....



I never thought I could finish what I started

Now I can

SEROQUEL is indicated for the treatment of acute manic episodes associated with bipolar I disorder and the treatment of schizophrenia. Patients should be periodically reassessed to determine the need for continued treatment.

In the elderly and in patients with hepatic impairment, consideration should be given to a lower starting dose, a slower rate of dose titration, careful monitoring during the initial dosing period, and a lower target dose.

Prescribing should be consistent with the need to minimize the risk of tardive dyskinesia, seizures, and orthostatic hypotension. A rare condition referred to as neuroleptic malignant syndrome (NMS) has been reported with this class of medications, including SEROQUEL.

There have been reports of diabetes mellitus and hyperglycemia-related adverse events associated with the use of atypical

In pivotal clinical trials, 7% of patients were 65 years or older.

The most commonly observed adverse events associated with the use of SEROQUEL in clinical trials were somnolence, dry mouth, dizziness, constipation, asthenia, abdominal pain, postural hypotension, pharyngitis, SGPT increase, dyspepsia, and weight gain.



Seroquel[®]
quetiapine fumarate
25 mg, 100 mg, 200 mg & 300 mg tablets

AstraZeneca 
AstraZeneca Pharmaceuticals LP

To prevent medication errors, write "**SEROQUEL**" clearly on your Rx pad. Spell "**SEROQUEL**" clearly over the phone.

Please see Brief Summary of Prescribing Information on following page.

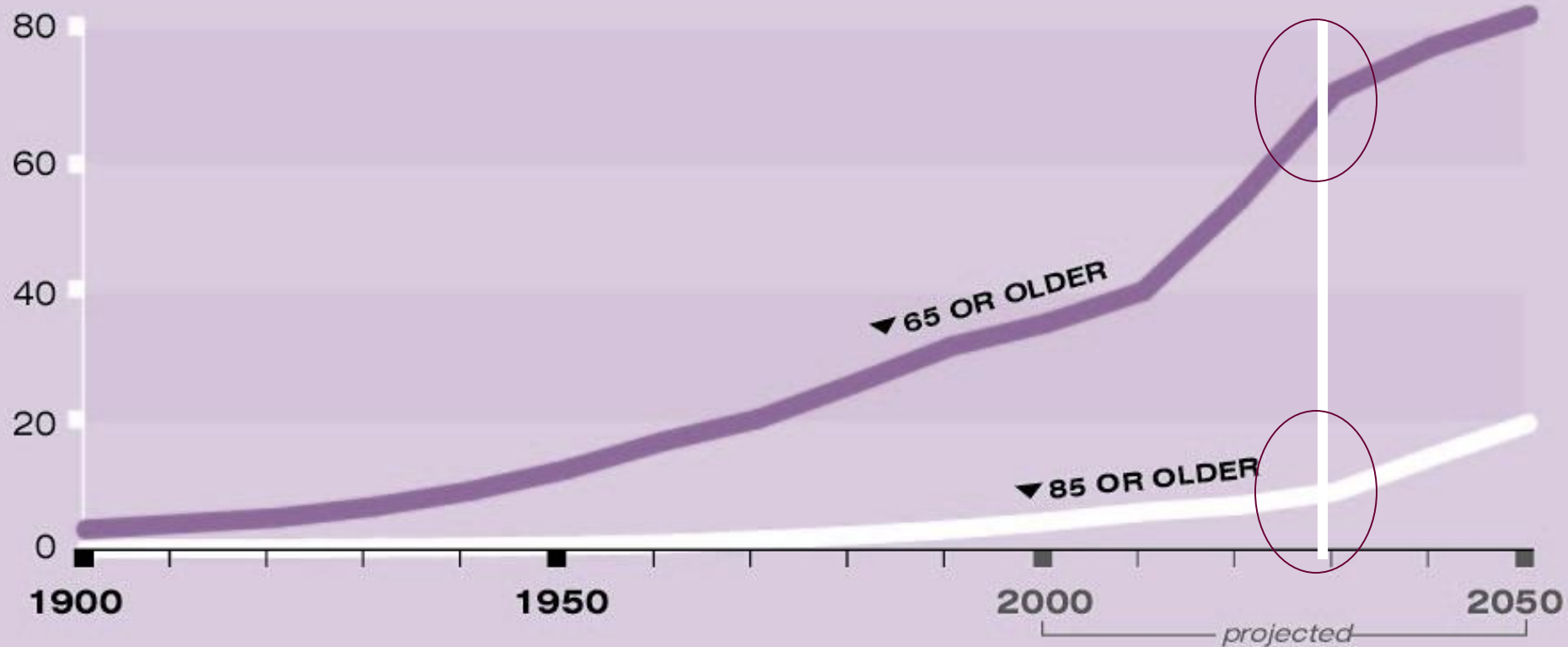
www.SEROQUEL.com

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Redefine Success

In pivotal clinical trials,
7% of patients were 65
years or older.

Total number of persons age 65 or older, by age group, 1900 to 2050, in millions



Note: Data for the years 2000 to 2050 are middle-series projections of the population.

Reference population: These data refer to the resident population.

Source: U.S. Census Bureau, Decennial Census Data and Population Projections.

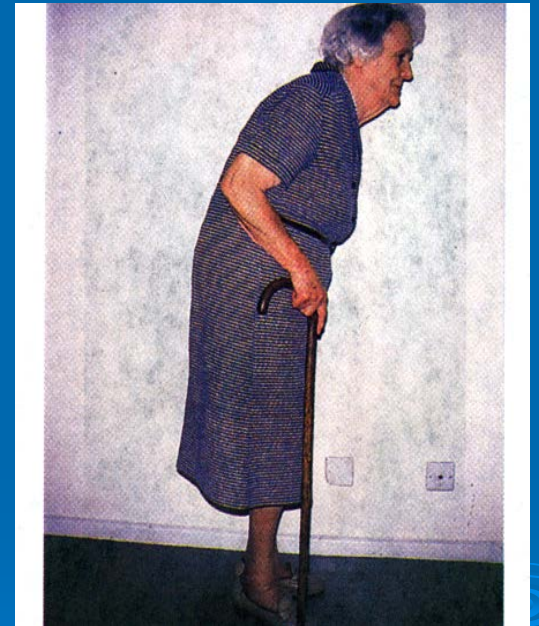
Heterogeneity of Aging



Fit



Vulnerable



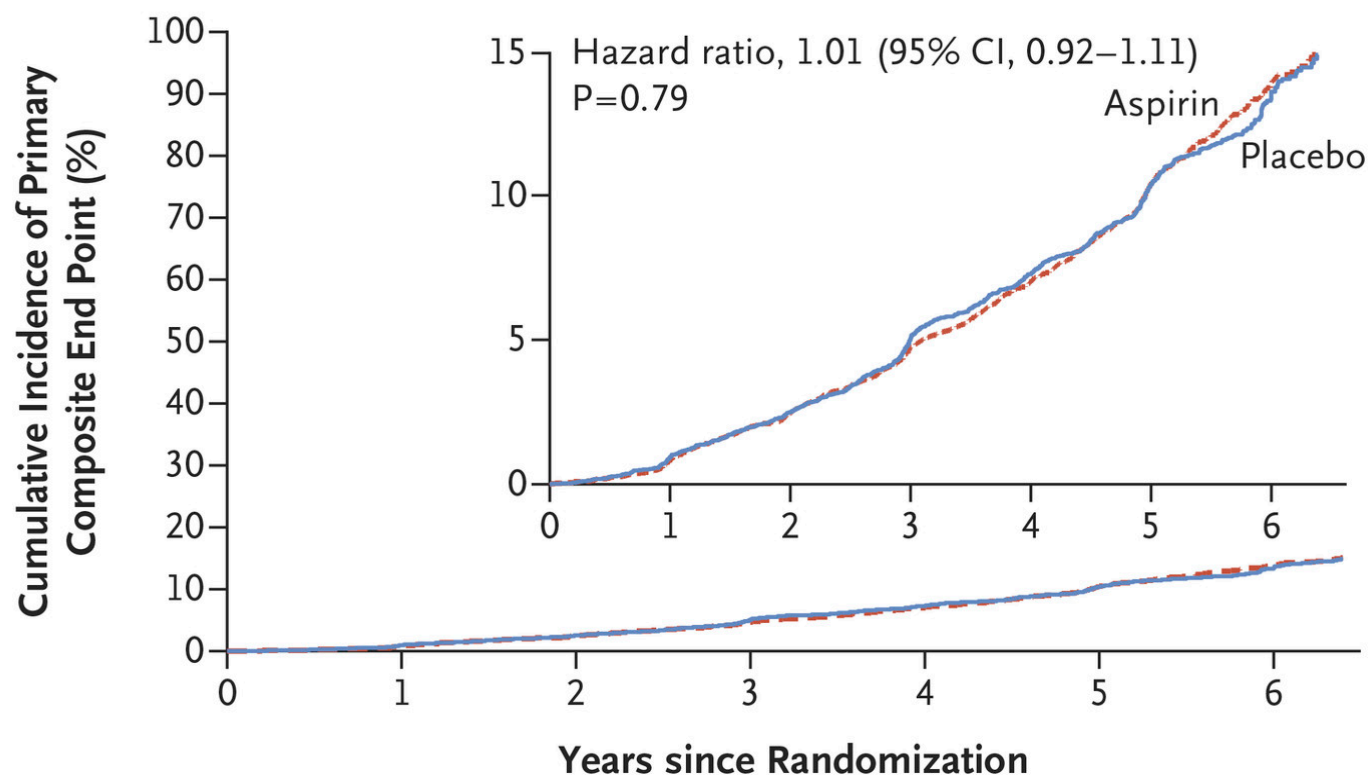
Frail

Can we extrapolate RCT results from young to old?

- RCT of 19,114 people in US and Australia; 2010-2014
- 65-73 yo: 50%; ≥ 74 yo: 50%
- Inclusions:
 - Community-dwelling
 - ≥ 70 , unless U.S. Black or Hispanic, then ≥ 65
 - No chronic illness (limit survival during 5 yrs), no CV or cerebrovascular disease
- Exclusions
 - Dementia or MMSE < 78
 - High risk of bleeding or ASA contraindication
 - Substantial physical disabilities (4-5 on ADLs, IADLs)
- Outcomes: Death, Dementia, Persistent Physical Disability

McNeil JJ et al. **ASPREE Trial (Aspirin in Reducing Events in the Elderly)**
NEJM 2018; 379;16: 1499-1508;1509-1518;1519-1528

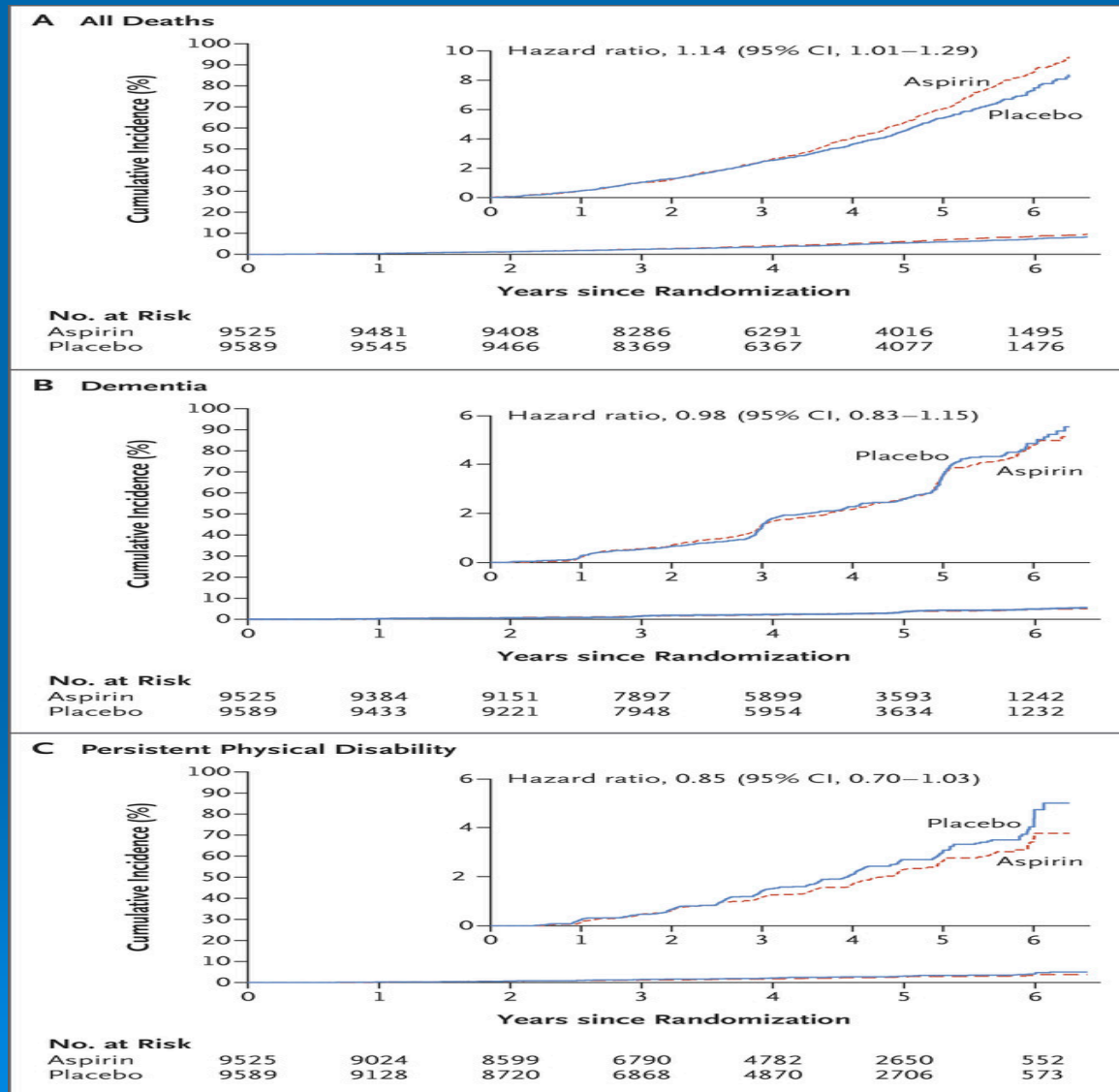
Cumulative Incidence of the Primary Composite End Point.



No. at Risk

Aspirin	9525	9432	9243	8026	6031	3763	1373
Placebo	9589	9484	9302	8077	6054	3790	1334

Cumulative Incidence of Death, Dementia, and Persistent Physical Disability.

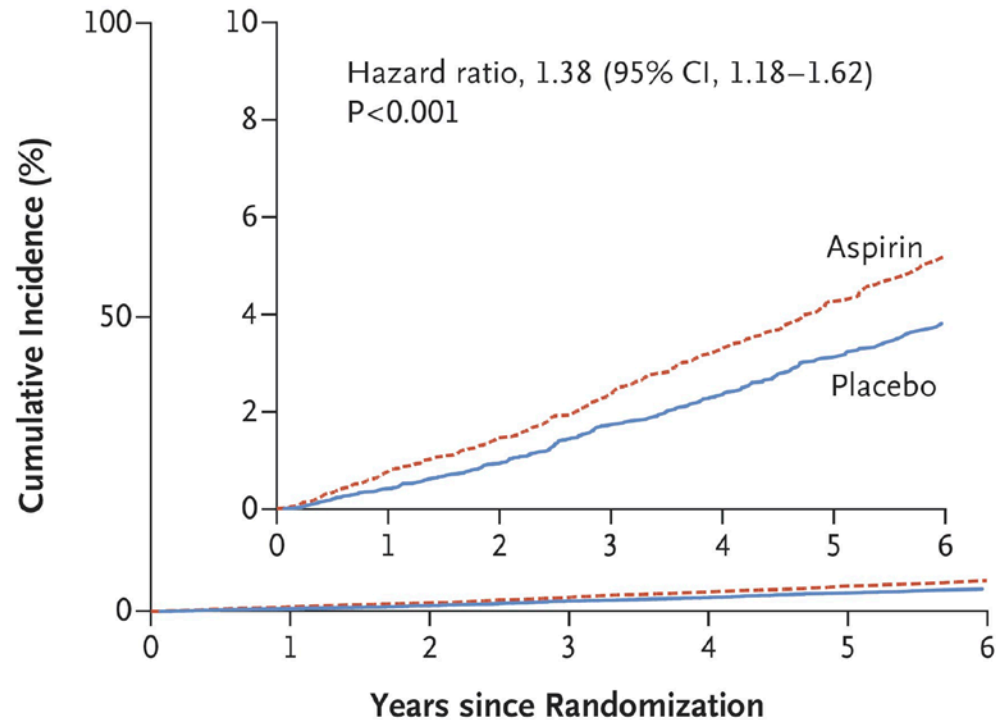


All Deaths

Dementia

Persistent
Physical
Disability

Cumulative Incidence of Major Hemorrhage



No. at Risk

Aspirin	9525	9337	9094	7833	5826	3574	1248
Placebo	9589	9424	9192	7930	5935	3632	1244

McNeil JJ et al. N Engl J Med 2018;379:1509-1518



The NEW ENGLAND
JOURNAL of MEDICINE

SPRINT TRIAL

- 2636 participants, mean age 79.9 yo
- SBP <120 mm Hg vs SBP <140 mm Hg
- **Primary outcome:** nonfatal MI, ACS w/o MI, nonfatal stroke, nonfatal acute decompensated HF, death from CV causes.
- **Follow-up median 3.4 years**
- **RESULTS: Less fatal and non-fatal CVEs and death from any cause with SBP <120**

SPRINT TRIAL and FRAILTY

- Higher event rates with increasing frailty, but intensive treatment group had lower absolute event rates
- Similar when stratified by gait speed
- However in secondary analysis for 80+, no benefit found in those with low MOCA scores (<18-20)

Ways to Determine Efficacy in Heterogeneous Older Adults

- Measure and analyze by constructs that may affect outcome , including adverse effects
 - Frailty
 - Cognitive impairment
 - Functional ability
 - h/o Falls
- Why is this not happening?
 - Not clear way which construct and tool to use
 - May need to use more than one tool
 - May require direct observation (\$\$\$\$)

Outcomes that matter for older adults

- Life vs death- not so much.
- Functional ability, Cognition, Falls, Frailty
- Important AND reproduceable
 - Disability
 - Is a social and environmental construct
 - Impairment may not be disabling if you can access/afford assistive devices, remodeling, etc
 - NH placement
 - Depends on whether you have resources to be able to age in place
 - 24/7 assistance, Financial, retrofit residence....

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Issues

- Need greater numbers and heterogeneity
 - Frailty
 - Cognitive impairment
 - Functional impairment
 - h/o Falls
- Analyze outcomes for above groups
- Use outcomes that are meaningful to patients and reproducible

Knowledge gap: which constructs and tools to use to capture heterogeneity