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

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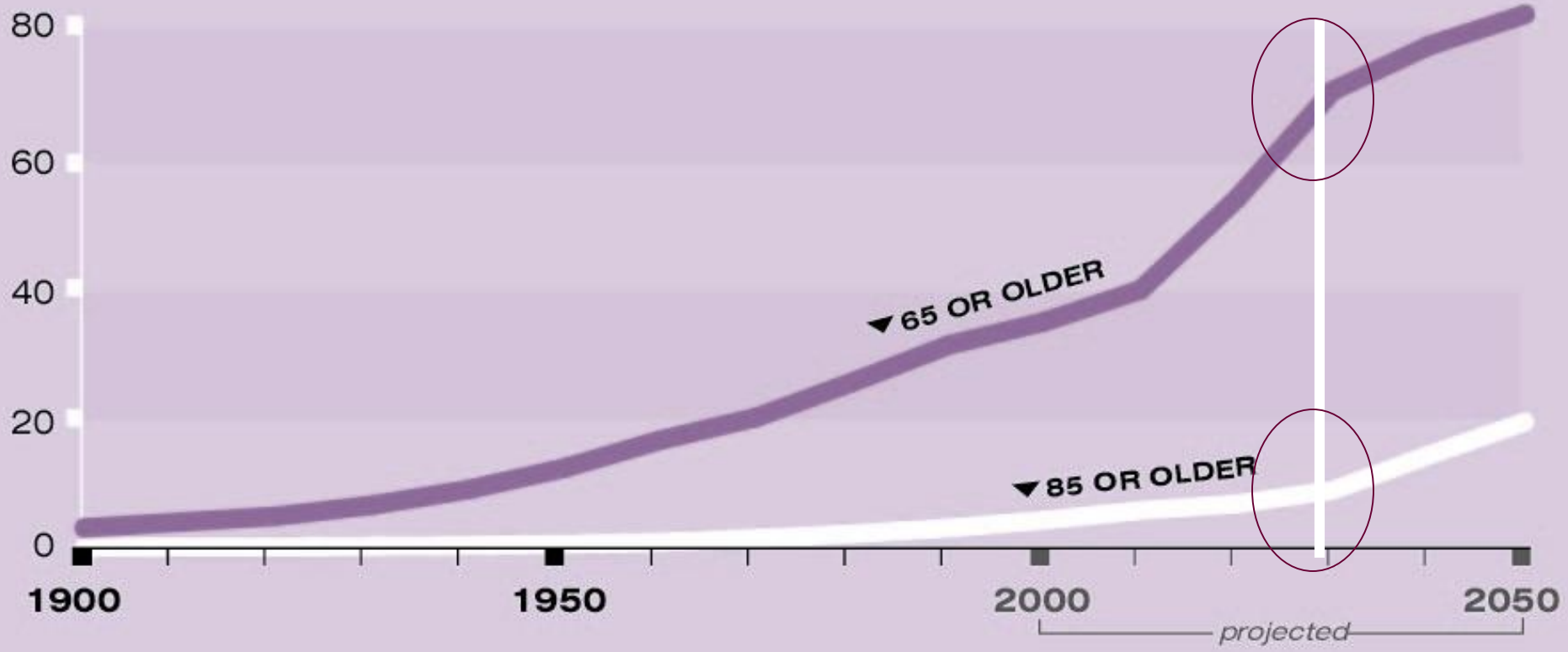
Randomized Controlled Drug Trials

- 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….

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

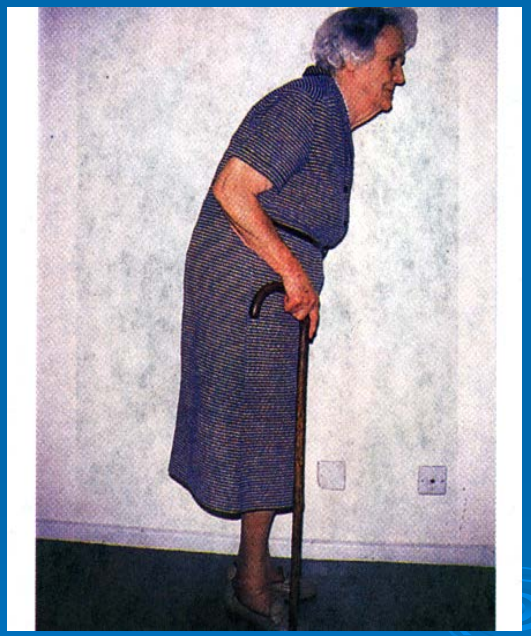


Note: Data for the years 2000 to 2050 are middle-series projections of the population.
Reference population: These data refer to the resident population.
Source: U.S. Census Bureau, Decennial Census Data and Population Projections.

Heterogeneity of Aging

Fit

Vulnerable



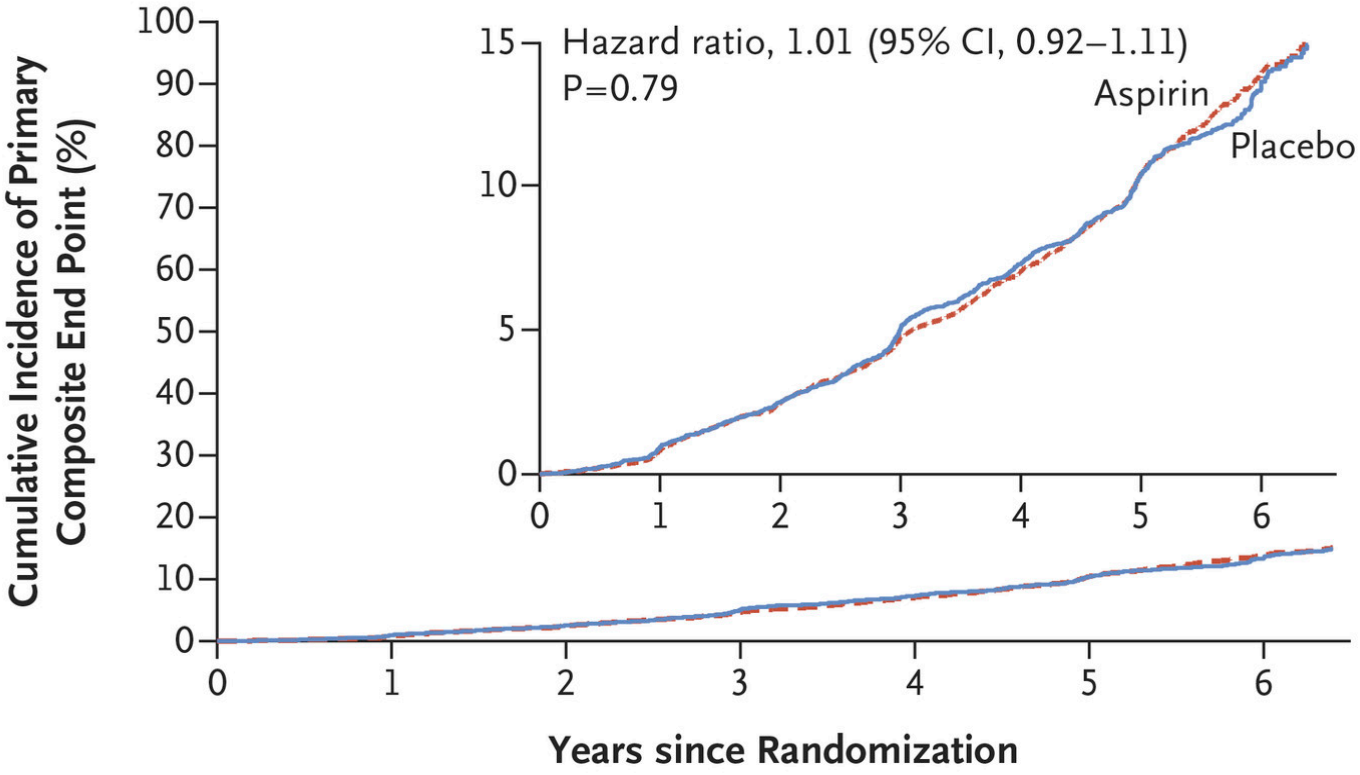
Frail

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 MMMSE <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.



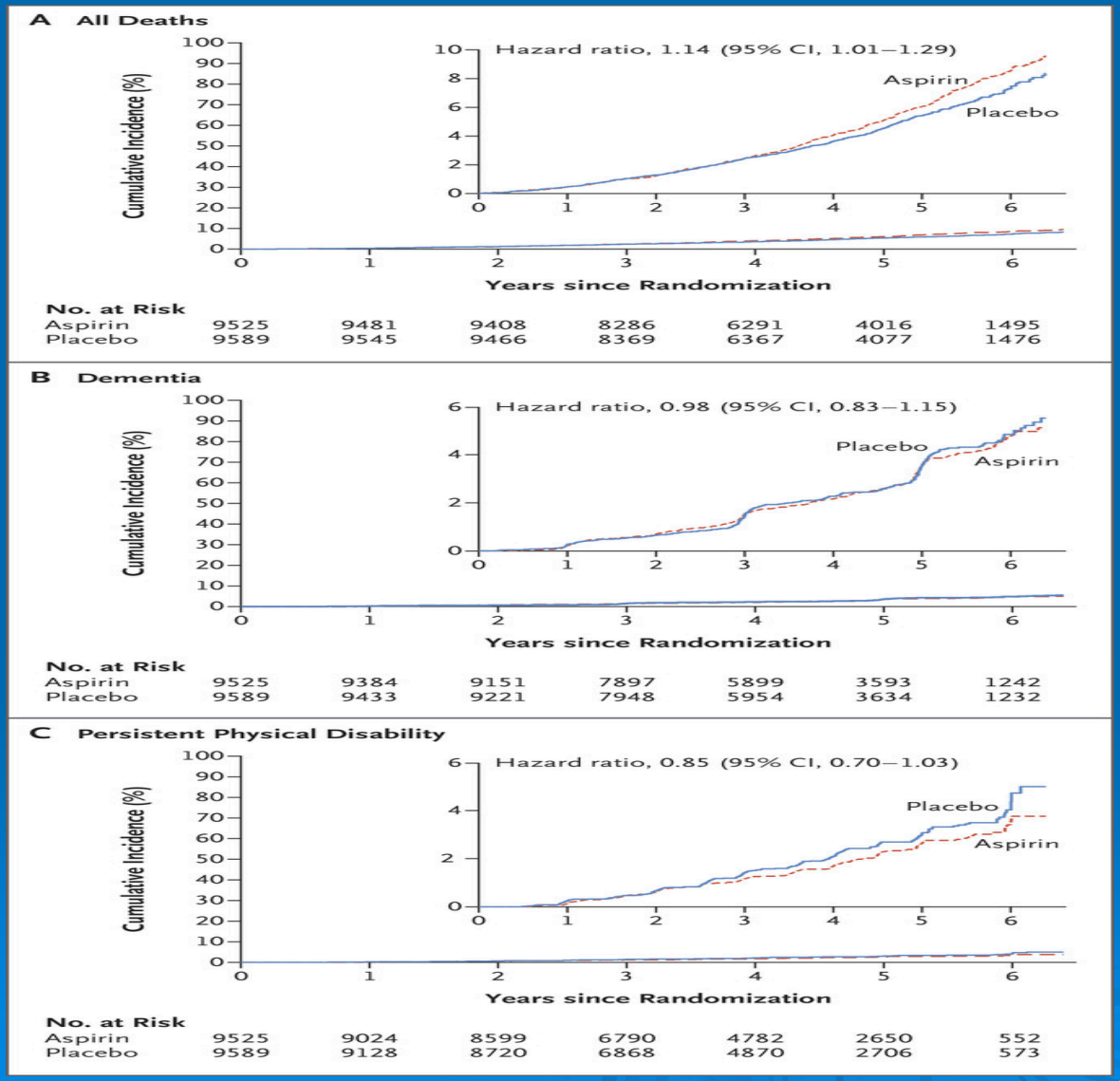
No. at Risk

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

JJ McNeil et al. N Engl J Med 2018;379:1499-1508.

The NEW ENGLAND JOURNAL of MEDICINE

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



All Deaths

Dementia

Persistent Physical Disability

JJ McNeil et al. N Engl J Med 2018;379:1499-1508.

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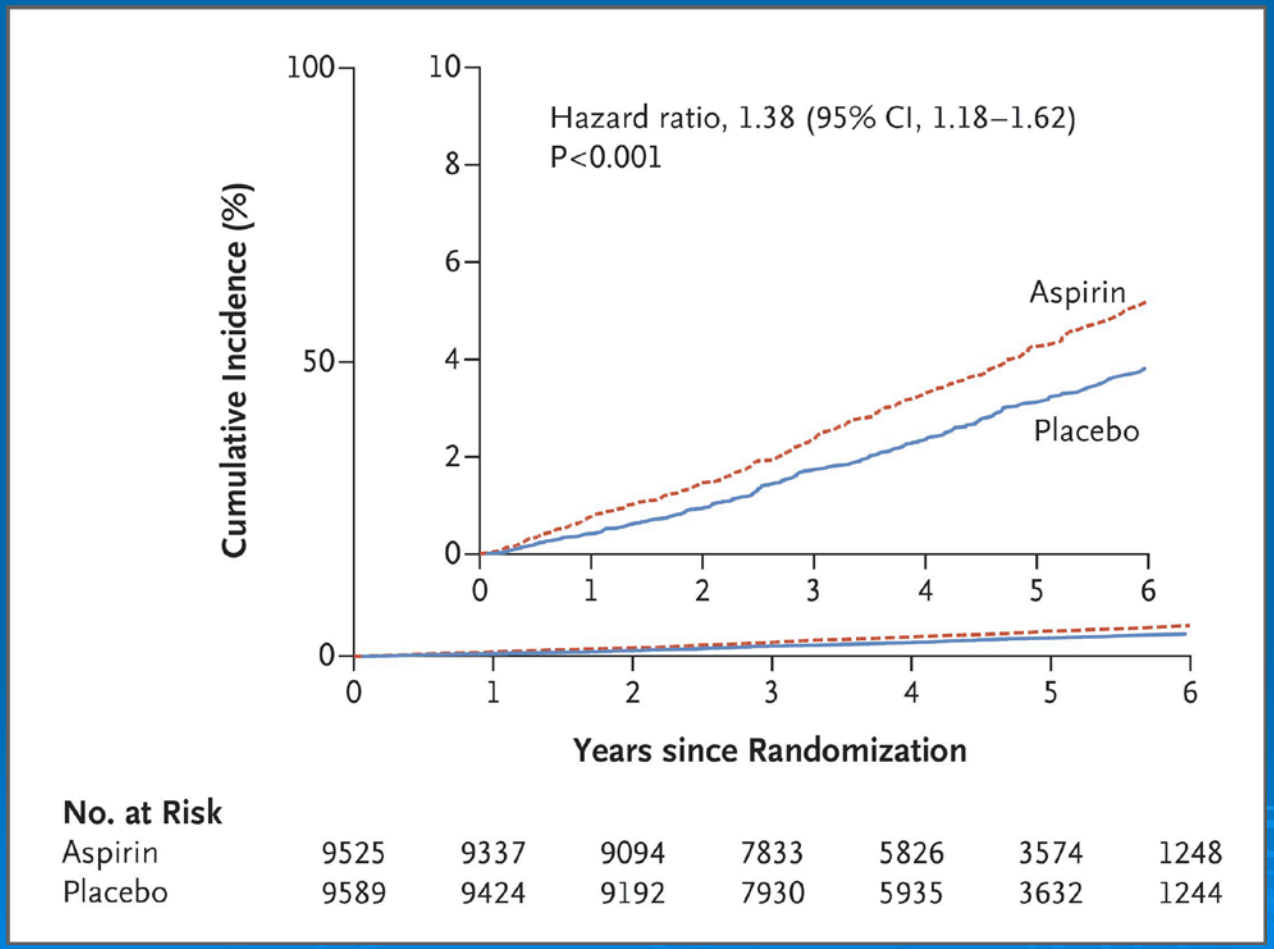
Cumulative Incidence of Major Hemorrhage



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

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SPRINT TRIAL

- **2636 participants, mean age 79.9 yo**
- **SBP <120 mm Hg vs SBP <140 mg 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**

Williamson JD et al. SPRINT. JAMA 2016; 3115(24):2673-2682

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)

Williamson JD et al. SPRINT. JAMA 2016; 3115(24):2673-2682
Pajewski NM, et al. Secondary analysis. JAGS 2020; 68:496-504

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 reproduceable

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