Extrapolating from fit to frail. Is it possible?

How to assess the efficacy of preventive strategies in older subjects

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I have no potential conflict of interest to report
Frailty is a state of increased vulnerability to poor resolution of homeostasis following a stress, which increases the risk of adverse outcomes including falls, delirium, disability and death.
Distinguishing features of frail older individuals when considering preventive strategies

- Different priorities
- Shorter life expectancy
- Lag time to benefit (when it will help?)
- Frailty may influence suitability, i.e. possibility to implement preventive strategies
- Frailty may influence the efficacy of the intervention
- Frailty may increase the risk of adverse events due to the intervention
Life expectancy in frail older adults
# Frailty and mortality risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>N. of participants</th>
<th>Length of follow-up</th>
<th>Mortality HR/OR 95% CI</th>
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<tr>
<td>Cardiovascular Health Study (CHS)</td>
<td>2001</td>
<td>US</td>
<td>5317</td>
<td>7 years</td>
<td>HR 1.32 1.13-1.55</td>
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<td>HR 1.63 1.27-2.08</td>
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<td>Canadian Study of Health and Aging (CSHA)</td>
<td>2004</td>
<td>Canada</td>
<td>9008</td>
<td>5 years</td>
<td>OR 2.54 1.92-3.37</td>
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<td>OR 3.69 2.26-6.02</td>
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<td>Women’s Health and Aging Study (WHAS)</td>
<td>2006</td>
<td>US</td>
<td>1438</td>
<td>3 years</td>
<td>HR 3.50 1.91-6.39</td>
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<td>HR 6.03 3.00-12.0</td>
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<tr>
<td>Study of Osteoporotic Fractures (SOF)</td>
<td>2008</td>
<td>US</td>
<td>6701</td>
<td>4.5 years</td>
<td>OR 1.54 1.40-1.69</td>
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<td>HR 2.75 2.46-3.07</td>
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*Clegg A., Lancet, 2013*
Changes in relative fitness and frailty across the adult lifespan: evidence from the Canadian National Population Health Survey

*Rockwood, CMAJ, 2011*

**Methods:** We analyzed data for community dwelling respondents (age 15–102 years at baseline) to the longitudinal component of the National Population Health Survey, with seven two-year cycles, beginning 1994–1995. The outcomes were death, use of health services and change in health status, measured in terms of a Frailty Index constructed from 42 self-reported health variables. Frailty was defined as a frailty index>0.21.
Changes in relative fitness and frailty across the adult lifespan: evidence from the Canadian National Population Health Survey

Rockwood, CMAJ, 2011

Results: The sample consisted of 14,713 respondents (54.2% women). Vital status was known for more than 99% of the respondents. The prevalence of frailty increased with age, from 2.0% (95% confidence interval [CI] 1.7%–2.4%) among those younger than 30 years to 22.4% (95% CI 19.0%–25.8%) for those older than age 65, including 43.7% (95% CI 37.1%–50.8%) for those 85 and older. At all ages, the 160-month mortality rate was lower among relatively fit people than among those who were frail (e.g., 2% v. 16% at age 40; 42% v. 83% at age 75 or older).
Transition of health state and mortality over 2, 4 and 12 years in people who were frail at baseline (n=1019)

Rockwood, CMAJ, 2011
Kaplan–Meier probability of survival over 12 years, according to baseline health status, for all respondents at least 15 years of age and 70 years or older

Rockwood, CMAJ, 2011
LE in each frailty state: robust, pre-frail, frail, disabled (with severe activity limitation) in absolute years and as a proportion of LE (15 EU countries combined), by sex and age.

Romero-Ortuno, Age and Ageing, 2014
What is the duration of life expectancy in the state of frailty? Estimates in the SIPAF study

Herr M, Eur J Ageing, 2017

The SIPAF study ("Système d’Information sur la Perte d’Autonomie Fonctionnelle de la personne âgée") included 2350 individuals aged 70 and over and living in France.

Participants were interviewed at home by trained nurses. Frailty was defined as impairment in three domains or more among nutrition, energy, physical activity, strength, and mobility.

People requiring assistance in basic activities of daily living were considered in a separate category.
Life expectancy by frailty state by 5-years age group in SIPAF STUDY

Herr M, Eur J Ageing, 2017
Lag time to benefit
(when it will help?)
“When Will it Help?” Incorporating Lagtime to Benefit into Prevention Decisions for Older Adults

“Lagtime to benefit” (LtB) is defined as the time between the preventive intervention to the time when improved health outcomes are seen.

Many standardized measures such as relative risk, odds ratio and absolute risk reduction quantify the magnitude of benefit (“How much will it help?”). However, the measures and methodologies to calculate a LtB (“When will it help?”) are underdeveloped and often not reported.
“When Will it Help?” Incorporating Lagtime to Benefit into Prevention Decisions for Older Adults

For older adults, the question “When will it help?” is just as important as “How much will it help?” If an older adult's life expectancy (LE) is substantially shorter than the LtB for a preventive intervention, performing that intervention exposes them to the immediate risks of the intervention with little likelihood of surviving long enough to benefit.

In addition, the factors associated with limited LE, such as increased age, comorbidities and functional limitations are strong risk factors for complications and side effects of interventions, further increasing the chances that prevention would harm rather than help these patients.
“When Will it Help?” Incorporating Lagtime to Benefit into Prevention Decisions for Older Adults

Juxtaposing an older patient's LE and the LtB may help clinicians identify which patients are more likely to be helped by a preventive intervention and which patients are more likely to be harmed.

1. Estimate patient’s life expectancy (LE) www.ePrognosis.com
2. Estimate the preventive intervention’s lagtime to benefit (LtB)
3.A If LE >> LtB, the intervention may help
3.B If LE << LtB, the intervention is more likely to harm
3.C If LE~LtB, the benefits vs harms of the preventive intervention are a “close call” and patient preferences (e.g. the degree of importance placed on the potential benefits and harms) should play the dominant role in decision making.
US Preventive Services Task Force (USPSTF) recommends routine colorectal cancer screening for older adults age 50-75. One reason is that the average LE for 75 year old Americans (11.1 years in 2000) is similar to the LtB for colorectal cancer screening (10.3 years). However, focusing on age rather than LE can lead to poor prevention decisions. ...a 70 year old man with oxygen-dependent lung disease and restricted mobility falls within the age range where routine colorectal cancer screening is recommended, but he has a limited LE and is unlikely to benefit from colorectal cancer screening. Conversely, an 80 year gentleman who walks 9 holes for golf weekly does not fall within the age range where colorectal cancer screening is recommended, but has a good chance of surviving to benefit from screening.
Frailty may influence the efficacy of the intervention

Vaccines
Immunological responses to pneumococcal vaccine in frail older people

AIM: To evaluate the immunogenicity of the 7-valent conjugated pneumococcal vaccine (PCV7) versus 23-valent polysaccharide vaccine (23vPPV) and compare the immune response to four serotypes (4, 6B, 18C and 19F), with respect to age or frailty in an elderly population of previously unvaccinated hospitalized patients.

METHOD: 241 patients aged 60 years and over, recruited between 16 May 2005 and 20 February 2006, were randomised to 23PPV or PCV7 vaccine. We measured Frailty Index (FI), Barthel index and the MMSE. Serotype-specific IgG was measured by ELISA at base line and 6 months after vaccination. Antibody responses were defined by the ratio of post-vaccination to pre-vaccination IgG antibody concentration (poor < 2-fold increase, acceptable > or = 2.0 to 3.99-fold and strong > or = 4.0-fold increase).
Immunological responses to pneumococcal vaccine in frail older people

RESULTS: Pre-immunization IgG was generally low and did not differ significantly by age or frailty. Post-immunization, IgG increased to all four serotypes; acceptable or strong response ranged between 29% for (6B) and 57% for (18C). There was no significant difference between the two vaccine types (23PPV versus PCV7). At 6 months post-vaccination, the highest geometric mean IgG concentrations (GMCs) were seen for serotype 19F and the lowest for serotype 4. Although there was some variation by serotype, responses after vaccination were lowest in the most frail or aged subjects.

CONCLUSIONS: Pneumococcal vaccines are perceived to offer low protection in the frail elderly, but our study showed that the proportion of this vulnerable population with acceptable responses is encouraging. Frailty, as measured by the Frailty Index, appears to be a better predictor of immune response to pneumococcal vaccines than age alone.
Frailty is associated with impairment of vaccine-induced antibody response and increase in post-vaccination influenza infection in community-dwelling older adults

Annual immunization with a trivalent inactivated vaccine (TIV) is considered efficacious for prevention of seasonal influenza in older adults. However, significant controversy exists in the current literature regarding the clinical effectiveness of TIV immunization in this highly heterogeneous population.

Frailty is an important geriatric syndrome characterized by decreased physiologic reserve and increased vulnerability to stressors. Using a validated set of frailty criteria, we conducted a prospective observational study to evaluate TIV-induced strain-specific hemagglutination inhibition (HI) antibody titers and post-vaccination rates of influenza-like illness (ILI) and infection in frail and nonfrail older adults.
Yao X, Vaccine. 2011
Efficacy and immunogenicity of high-dose influenza vaccine in older adults by age, comorbidities, and frailty

*DiazGranados CA, Vaccine 2015*

**BACKGROUND:** A randomized trial demonstrated that a high-dose inactivated influenza vaccine (IIV-HD) was 24.2% more efficacious than a standard-dose vaccine (IIV-SD) against laboratory-confirmed influenza illness in adults ≥65 years. To evaluate the consistency of IIV-HD benefits, supplemental analyses explored efficacy and immunogenicity by baseline characteristics of special interest.

**METHODS:** Double-blind, randomized, active-controlled, multicenter trial. Adults ≥65 years were randomized 1:1 to receive IIV-HD or IIV-SD and followed for 6-8 months postvaccination for the occurrence of influenza. One third of participants were randomly selected to provide sera for measurement of hemagglutination inhibition antibody (HAI) titers. Efficacy (IIV-HD vs. IIV-SD) against laboratory-confirmed, protocol-defined influenza-like illness (PD-ILI) and HAI geometric mean titer (GMT) ratios (IIV-HD/IIV-SD) were evaluated by age, and number of high-risk comorbid and frailty conditions.
Efficacy and immunogenicity of high-dose influenza vaccine in older adults by age, comorbidities, and frailty

**RESULTS:**
Efficacy (95% confidence intervals) of IIV-HD relative to IIV-SD against laboratory-confirmed PD-ILI was 19.7% (0.4%; 35.4%) for participants 65-74 years, 32.4% (8.1%; 50.6%) for those ≥75 years, 22.1% (3.9%; 37.0%) for participants with ≥1 high-risk comorbidity, 23.6% (-3.2%; 43.6%) for those with ≥2 high-risk comorbidities, 27.5% (0.4%; 47.4%) for persons with 1 frailty condition, 23.9% (-9.0%; 47.2%) for those with 2 frailty conditions, and 16.0% (-16.3%; 39.4%) for those with ≥3 frailty conditions. There was no evidence of vaccine efficacy heterogeneity within age, comorbidity, and frailty strata (P-values 0.351, 0.875, and 0.838, respectively). HAI GMT ratios were significantly higher among IIV-HD recipients for all strains and across all subgroups.
Efficacy and immunogenicity of high-dose influenza vaccine in older adults by age, comorbidities, and frailty

DiazGranados CA, Vaccine 2015

CONCLUSIONS:
Estimates of relative efficacy consistently favored IIV-HD over IIV-SD. There was no significant evidence that baseline age, comorbidity, or frailty modified the efficacy of IIV-HD relative to IIV-SD. IIV-HD significantly improved HAI responses for all strains and in all subgroups. IIV-HD is likely to provide benefits beyond IIV-SD for adults ≥65 years, irrespective of age and presence of comorbid or frailty conditions.
Frailty may exacerbate adverse effects of therapy
Anticoagulants
The prevalence of AF increases with age.

Lifetime risk for developing atrial fibrillation (AF) from the Framingham Heart Study. Men and women without AF at 40 years of age were determined to have a 26 and 23 percent likelihood of developing incident AF by 80 years of age.
TREATMENT OPTIONS

Historically, vitamin K antagonists, such as warfarin, were the only anticoagulants widely available for human use. It has been estimated that more than 65,000 patients are treated in U.S. emergency departments (ED) annually for warfarin-related hemorrhage. Because of this high rate of bleeding, along with the drug’s narrow therapeutic index and the need for frequent monitoring, there has been a desire to create safer anticoagulants without such strict drug monitoring.

Harter K., Western Journal of Emergency Medicine, 2015
The impact of frailty on the utilisation of antithrombotic therapy in older patients with atrial fibrillation

*Perera V, Age Aging, 2009*

**OBJECTIVE:** to investigate the impact of frailty on the utilisation of antithrombotics and on clinical outcomes in older people with atrial fibrillation (AF).

**DESIGN:** prospective study of a cohort of 220 acute inpatients aged > or =70 years with AF, admitted to a teaching hospital in Sydney, Australia (April-July 2007), with 207 followed up over 6 months.

**RESULTS:** a total of 140 patients (64%) were identified as frail using a validated tool. Frail patients were less likely to receive warfarin than non-frail on hospital admission (P = 0.002) and discharge (P < 0.001). During hospitalisation, the proportion of frail participants prescribed warfarin decreased by 10.7% and that of non-frail increased by 6.3%. Over the 6-month follow-up, 43 major or severe haemorrhages (20.8%), 20 cardioembolic strokes (9.7%) and 40 deaths (19.2%) were reported. Compared to non-frail, frail participants were significantly more likely to experience embolic stroke (RR 3.5, 95% CI 1.0-12.0, P < 0.05), had a small non-significant increase in risk of major haemorrhage (RR 1.5, 95% CI = 0.7-3.0, P = 0.29) and had greater mortality (RR 2.8, 95% CI 1.2-6.5, P = 0.01).
The impact of frailty on the utilisation of antithrombotic therapy in older patients with atrial fibrillation

CONCLUSION:
Frail older inpatients with AF are significantly less likely to receive warfarin than non-frail and appear more vulnerable to adverse clinical outcomes, with and without antithrombotic therapy.

Perera V, Age Aging, 2009
NOACs

**ADVANTAGES**
- Fixed dosage
- No dietary restrictions
- No necessity of monitoring
- Few interactions with drugs

**DISADVANTAGES**
- Anticoagulant effect more difficult to evaluate and monitor
- Therapeutical adherence more difficult to measure
- Antidotes
- Severe chronic renal failure
Representativeness of the dabigatran, apixaban and rivaroxaban clinical trial populations to real-world atrial fibrillation patients in the United Kingdom: a cross-sectional analysis using the General Practice Research Database

Lee S., BMJ Open. 2012

OBJECTIVE: Three oral anticoagulants have reported study results for stroke prevention in patients with atrial fibrillation (AF) (dabigatran etexilate, rivaroxaban and apixaban); all demonstrated superiority or non-inferiority compared with warfarin (RE-LY, ARISTOTLE and ROCKET-AF). This study aimed to assess the representativeness for the real-world AF population, particularly the population eligible for anticoagulants.

DESIGN: A cross-sectional database analysis. Dataset derived from the General Practice Research Database (GPRD).

PRIMARY AND SECONDARY OUTCOMES MEASURE: The proportion of real-world patients with AF who met the inclusion/exclusion criteria for RE-LY, ARISTOTLE and ROCKET-AF were compared. The results were then stratified by risk of stroke using CHADS(2) and CHA(2)DS(2)-VASc.
Representativeness of the dabigatran, apixaban and rivaroxaban clinical trial populations to real-world atrial fibrillation patients in the United Kingdom: a cross-sectional analysis using the General Practice Research Database

Lee S., BMJ Open. 2012

RESULTS: 83 898 patients with AF were identified in the GPRD. For the population at intermediate or high risk of stroke and eligible for anticoagulant treatment (CHA(2)DS(2)-VASc ≥1; n=78 783 (94%)), the proportion eligible for inclusion into RE-LY (dabigatran etexilate) was 68% (95% CI 67.7% to 68.3%; n=53 640), compared with 65% (95% CI 64.7% to 65.3%; n=51 163) eligible for ARISTOTLE (apixaban) and 51% (95% CI 50.7% to 51.4%; n=39 892) eligible for ROCKET-AF (rivaroxaban). Using the CHADS(2) method of risk stratification, for the population at intermediate or high risk of stroke and eligible for anticoagulation treatment (CHADS(2) ≥1; n=71 493 (85%)), the proportion eligible for inclusion into RE-LY was 74% (95% CI 73.7% to 74.3%; n=52 783), compared with 72% (95% CI 71.7% to 72.3%; n=51 415) for ARISTOTLE and 56% (95% CI 55.6% to 56.4%; n=39 892) for ROCKET-AF.
Representativeness of the dabigatran, apixaban and rivaroxaban clinical trial populations to real-world atrial fibrillation patients in the United Kingdom: a cross-sectional analysis using the General Practice Research Database

CONCLUSIONS: Patients enrolled within RE-LY and ARISTOTLE were more reflective of the 'real-world' AF population in the UK, in contrast with patients enrolled within ROCKET-AF who were a more narrowly defined group of patients at higher risk of stroke.

LIMITATIONS: It should be noted that a number of the criteria included in the trial design for RE-LY, ARISTOTLE and ROCKET-AF were not recorded in the GPRD or were difficult to extract. For example, planned major surgery would not be captured within the database, nor would a life expectancy of less than 1 year, both of which are exclusion criteria in one or more of the trials.
Effectiveness and safety of oral anticoagulants in older patients with atrial fibrillation: a systematic review and meta-regression analysis

Bai Y., Age and Ageing 2017

Background and objective:
The study analysed the effectiveness and safety of warfarin use compared with warfarin nonuse and non-vitamin K antagonist oral anticoagulants (NOACs) in atrial fibrillation (AF) patients aged≥65 years.

Methods:
After searching PubMed and the Cochrane Library, 26 studies were included, with 10 comparing warfarin with warfarin non-use and 16 comparing warfarin with NOACs, in older AF patients (≥65years).
Effectiveness and safety of oral anticoagulants in older patients with atrial fibrillation: a systematic review and meta-regression analysis

Bai Y., Age and Ageing 2017

**Results:** warfarin use was superior to no antithrombotic therapy [relative risk (RR) 0.59, 95% CI 0.51–0.76, I² = 12.3%, n = 8] and aspirin (RR 0.44, 95% CI 0.24–0.64, I² = 0.0%, n = 5) for stroke/thromboembolism (TE) prevention. Warfarin use was associated with a non-significant increase in risk of major bleeding compared with no antithrombotic therapy (RR 1.26, 95% CI 0.99–1.52, I² = 0.0%, n = 7) and aspirin (RR 1.20, 95% CI 0.91–1.50, I² = 0.0%, n = 5). NOACs were superior to warfarin for stroke/TE prevention [hazard ratio (HR) 0.81, 95% CI 0.73–0.89, I² = 56.6%, n = 9], and also were associated with reduced risk of major bleeding compared to warfarin (HR 0.87, 0.77–0.97, I² = 86.1%, n = 9).

**Conclusions:** warfarin use was superior to warfarin non-use, aspirin and no antithrombotic therapy in reducing the risk of stroke/TE in older AF patients, but with a possible increase in major bleeding. NOACs were superior to warfarin for stroke/TE prevention, with reduced risk of major bleeding.
Weighted regression of RR of stroke/TE

Bai Y., Age and Ageing 2017
Risk of stroke/TE in AF patients aged ≥65 years comparing NOACs (namely dabigatran, rivaroxaban, apixaban and edoxaban) with warfarin.

Bai Y., Age and Ageing 2017
Subgroup analysis of Dabigatran, Apixaban, Rivaroxaban and Edoxaban vs Warfarin in risk of stroke/TE in AF patients with elderly age (≥65 years).

Bai Y., Age and Ageing 2017
Weighted regression of RR of major bleeding

Bai Y., Age and Ageing 2017
Risk of major bleeding in AF patients aged ≥65 years comparing NOACs (namely dabigatran, rivaroxaban, apixaban and edoxaban) with warfarin.

Bai Y., Age and Ageing 2017
Subgroup analysis of Dabigatran, Apixaban, Rivaroxaban and Edoxaban vs. Warfarin in risk of major bleeding in AF patients with elderly age (≥65 years)

Bai Y., Age and Ageing 2017
Efficacy and safety of oral anticoagulants in frail elderly patients with atrial fibrillation: an unsolved problem

At present, the efficacy and safety of anticoagulants, warfarin or NOAC in frail patients remain unknown, as these patients have largely been excluded from both randomized trials and “real-world” studies; as a result, the guidelines do not provide guidance for the management of this population. Frail patients with AF are significantly less likely to receive oral anticoagulants compared to their nonfrail counterparts; is that an expression of reasonable prudence or malpractice? ......Prospective “real-world” studies including frail AF patients are necessary. Waiting for more evidence, the doubt whether to prescribe or not an oral anticoagulant to frail AF patients remains legitimate.

Alboni P., G Ital Cardiol 2017
Conclusions

• The efficacy of preventive strategies and interventions cannot be extrapolated from the fit to the frail elderly
• The peculiarity of frail older subjects call for specific studies, at least in real life setting, to evaluate preventive strategies
• Geriatricians should individualize preventive intervention to each frail older person