The association of artificial intelligence-enabled electrocardiogram-derived age (physiologic age) with atherosclerotic cardiovascular events in the community

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Background: We have demonstrated that artificial intelligence interpretation of ECGs (AI-ECG) can estimate an individual's physiologic age and that the gap between AI-ECG and chronologic age (Age-Gap) is associated with increased mortality. We hypothesized that Age-Gap would predict long-term atherosclerotic cardiovascular disease (ASCVD) and that Age-Gap would refine the ACC/AHA Pooled Cohort Equations' (PCE) predictive abilities.

Methods: Using the Rochester Epidemiology Project (REP) we evaluated a community-based cohort of consecutive patients seeking primary care between 1998–2000 and followed through March 2016. Inclusion criteria were age 40–79 and complete data to calculate PCE. We excluded those with known ASCVD, AF, HF or an event within 30 days of baseline.A neural network, trained, validated, and tested in an independent cohort of ~ 500,000 independent patients, using 10-second digital samples of raw, 12 lead ECGs. PCE was categorized as low<5%, intermediate 5–9.9%, high 10–19.9%, and very high≥20%. The primary endpoint was ASCVD and included fatal and non-fatal myocardial infarction and ischemic stroke; the secondary endpoint also included coronary revascularization [Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Graft (CABG)], TIA and Cardiovascular mortality. Events were validated in duplicate. Follow-up was truncated at 10 years for PCE analysis. The association between Age-Gap with ASCVD and expanded ASCVD was assessed with cox proportional hazard models that adjusted for chronological age, sex and risk factors. Models were stratified by PCE risk categories to evaluate the effect of PCE predicted risk.

Results: We included 24,793 patients (54% women, 95% Caucasian) with mean follow up of 12.6±5.1 years. 2,366 (9.5%) developed ASCVD events and 3,401 (13.7%) the expanded ASCVD. Mean chronologic age was 53.6±11.6 years and the AI-ECG age was 54.5±10.9 years, R2=0.7865, p<0.0001. The mean Age-Gap was 0.87±7.38 years. After adjusting for age and sex, those considered older by ECG, compared to their chronologic age had a higher risk for ASCVD when compared to those with <–2 SD age gap (considered younger by ECG). (Figure 1A), with similar results when using the expanded definition of ASCVD (data not shown). Furthermore, Age-Gap enhanced predicted capabilities of the PCE among those with low 10-year predicted risk (<5%): Age and sex adjusted HR 4.73, 95% CI 1.42–15.74, p-value=0.01 and among those with high predicted risk (>20%) age and sex adjusted HR 6.90, 95% CI 1.98–24.08, p-value=0.0006, when comparing those older to younger by ECG respectively (Figure 1B).

Conclusion: The difference between physiologic AI-ECG age and chronologic age is associated with long-term ASCVD, and enhances current risk calculators (PCE) ability to identify high and low risk individuals. This may help identify individuals who should or should not be treated with newer, expensive risk-reducing therapies.

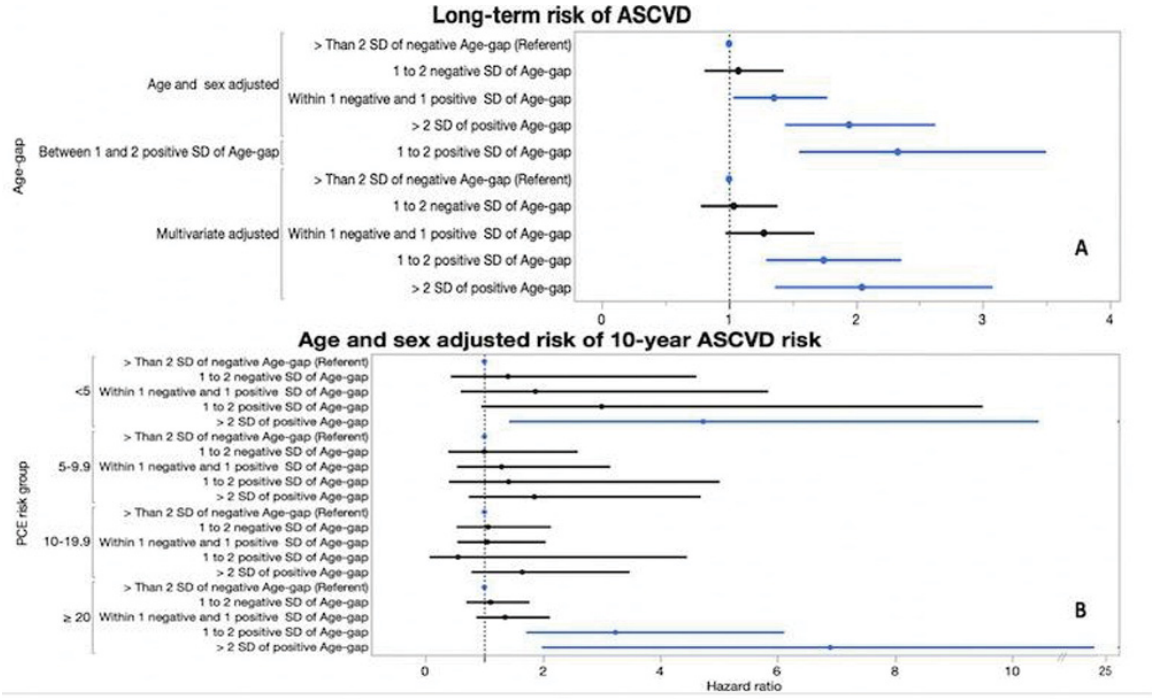

Figure 1: Cox Proportional Hazard Models Testing the Association Between Artificial Intelligence Enabled Electrocardiogram Derived Age with Atherosclerotic Cardiovascular Events in the Community. SD represents standard deviation of age-gap (~7.4 years); A negative age-gap denotes an individual identified as older by ECG when compared to chronological age, a positive age-gap denotes an individual identified as younger by ECG compared to chronological age. In **(A)** multivariate models adjust for age, sex, body mass index, systolic blood pressure, total and HDL cholesterol, history of dyslipidemia, diabetes, hypertension and current smokers. In **(B)** PCE predicted risk was categorized as low<5%, intermediate 5-9.9%, high 10-19.9%, and very high≥20% at the time of the ECG. Those with more than 2 SD of positive Age-gap are the referent group.