Challenges of treating cardiovascular risk in old age

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The need for pharmacotherapy for cardiovascular disease (CVD) prevention is recommended to be based on the assessment of total risk, accounting for several risk factors. This assessment aims to better identify individuals in primary prevention, for whom the risk is not yet confirmed by manifest CVD. Various risk calculators have been developed: the European Systematic Coronary Risk Evaluation chart (SCORE) and national calculators such as the UK-recommended QRISK2 CVD risk-prediction tool and its derivative QRISK3. In addition to traditional risk factors such as smoking, cholesterol levels, and blood pressure, QRISK3 also includes several items such as atrial fibrillation and chronic kidney disease.

Prediction is always challenging. Consequently, risk-prediction tools have their handicaps; for example, the 5–10 year absolute risk score in younger individuals is an under-prediction of their lifetime risk for a slowly developing disease such as CVD.[1] Another handicap is that many prediction score systems are not tailored to people older than 65–79 years (QRISK3 is designed for people aged up to 84 years). Moreover, most older people have high calculated risk on account of their age alone (reflecting time of accumulated risk), possibly leading to unnecessary medicalisation of old age. Another aspect related to older age is competing risk: those with high CVD risk could nevertheless die of something else. Finally, several traditional risk factors, such as cholesterol levels, blood pressure and body-mass index (BMI), might have weakened predictive power in old age because of reverse epidemiology.

In *The Lancet Healthy Longevity*, Shona Livingstone and colleagues have made a laudable contribution to the examination of the effects of CVD (including coronary heart disease and stroke) risk prediction in old age for primary prevention.[2] The authors externally validated the QRISK3 tool using Clinical Practice Research Datalink data and including in the study population 1 484 597 women and 1 420 176 men aged 25–84 years with no previous history of CVD or statin treatment. Livingstone and colleagues compared the QRISK3-predicted 10-year CVD risk with the observed 10-year risk in the whole population and in important subgroups, including older people and people with multimorbidity, and they examined the discrimination and calibration of QRISK3 with and without accounting for competing risks.

The authors found that, although QRISK3 performed well at the whole population level (Harrell's C-statistic 0·865 in women and 0·834 in men), prediction was suboptimal in older people (<0·65 in all subgroups aged 65 years or older). The findings showed over-prediction of risk in older adults, especially when competing risks were not considered. One of the study's conclusions was that clinicians should very carefully consider the use of preventive drugs such as statins in people with comorbidities.

For **SCORE** see https://www.heartscore.org/

For **QRISK3** see https://qrisk.org/three

My aim here is not to criticise the results of this carefully done analysis, but rather to put results into perspective with regards to other factors related to older age. First, competing deaths could be ultimately due to the same root causes as coronary heart disease and stroke. Dementia can have vascular origins and CVD treatment can prevent it;[3] falls and injuries can—at least indirectly—have connection to vascular disease; smoking predisposes to CVD as well as cancer. Geriatric syndromes, such as frailty, could be the cause of death, but it is not usually diagnosed as CVD. However, as shown in a UK Biobank study, CVD risk factor status measured at age 63 years also predicted geriatric syndromes during a 10-year follow-up.[4] Consequently, using fatal coronary heart disease or stroke alone as an endpoint in the analysis might lead to underestimation of the real impact of CVD risk factors in older people.

Second, some seeming paradoxes complicate the assessment of risk factors measured in old age. On one hand, individuals who were overweight in midlife might have lost weight and be therefore normal weight in old age, but they can still be at higher risk of CVD and mortality than individuals who have gained weight after midlife.[5] On the other, high cholesterol levels remain a risk factor also in old age, if endogenous causes of cholesterol lowering (such as frailty) are not taken into account, showing the importance of considering age-related confounders for ascertaining risk factors in old age.[5] Additionally, a long follow-up might lead to over-prediction of baseline risk factors, if post-baseline treatments improve prognosis.

Third, one important goal of CVD risk prediction has been to restrict statin treatment. This goal is driven by

two main reasons. After their introduction in 1987, statins were expensive drugs and targeting treatment was motivated by cost-effectiveness. Currently, statins are cheap and might be cost-saving. A more recent problem of statins has been fear of adverse effects. However, these are often due to a nocebo effect, according to a recent analysis showing that about 90% of cases were attributable to a nocebo effect.[6] Several observational studies have also indicated that older people using statins have better prognoses than those not using statins, even irrespective of frailty.[7] A careful consideration of both benefits and potential harms of statin treatment is nevertheless warranted in vulnerable patients, who often have competing risks and polypharmacy.

Because of problems with risk prediction in old age, a more reliable way to find out whether a risk factor is important is to treat it. According to clinical trials, lowering blood pressure is beneficial even after age 80 years, but individual factors such as frailty and functional status need to be taken into account.[8] A meta-analysis of statin trials suggested that treatment is beneficial after age 75 years, although the benefit in primary prevention is less certain.[9] More trial evidence of statins in primary prevention for individuals aged 70 years or older will become available from the large Study of Statins for Reducing Events in the Elderly (STAREE) in 2023.

For the **STAREE trial** see https://clinicaltrials.gov/ct2/show/NCT02099123

Finally, a provocative way to circumvent problems with inaccurate risk prediction was presented 18 years ago. Because a large number of people exposed to low risk is likely to produce more cases than a small number exposed to a high risk, as posited by Geoffrey Rose, Nicholas Wald and Malcolm Law translated this axiom into a polypill strategy: administration of a combination of CVD preventive drugs for all people aged 55 years or older without formal risk assessment.[10] With accumulating empirical data, this idea is gradually gaining acceptance, especially if combined with more targeted methods, such as coronary artery calcium score, to exclude people with the lowest risk.[10]

All that said, one important message of the analysis of Livingstone and colleagues is that it once more reminds us that older people are a heterogenous group, and individualised decisions are often needed.

I have received consulting fees from Amgen, Boehringer, GlaxoSmithKline, Novartis, Nutricia, Orion, Roche, Sankyo, and Sanofi, outside the submitted work. I have participated (without financial compensation) in the preparation of Finnish national guidelines for hypertension, obesity, and dyslipidaemia.

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