Abstract accepted for the 92nd congress of the European Atherosclerosis Society (EAS), Lyon, May 26-29, 2024

Machine Learning to Optimize Statin Therapy using Real-World Primary Care Outcomes: Can Statin Doses be Reduced in Some Patients?

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Background and Aims
Clinical guidelines for cholesterol lowering are based on interventional clinical trials conducted in selected patient cohorts. Guidelines applicable to the majority of patients may not be optimal for all patients. We tested the hypothesis that machine learning could identify individuals in a UK primary care setting for whom personalised cholesterol-lowering therapy might be more appropriate than guideline-based recommendations.

Methods
A neural network was created that accurately reproduced UK national clinical guidelines for cholesterol lowering, i.e., National Institute for Health and Care Excellence (NICE) CG67. A transfer learning procedure was then applied which refined the guidance using retrospective real-world outcomes recorded in the anonymized national UK primary care Clinical Practice Research Datalink electronic health record resource. Similar features (Shapley values derived from game theory) were used to define a digital twin cohort for each recommendation that deviated from the guidelines and were justified by rejecting the no-benefit hypothesis at $p>0.01$.

Results
Adult patients (n=9,675) receiving statin therapy (mean $\pm$ SD age 74 $\pm$ 11 yr; M 54% vs F 46%; primary prevention 65% vs secondary prevention 35%) with complete records were identified. The prevalence of major comorbidities, i.e., hypertension (71%) and type 2 diabetes (21%), was similar between the primary and secondary prevention cohorts. Learning from real-world outcomes when NICE treatment goals were achieved or not (>40% reduction in non-high-density lipoprotein cholesterol from pre-treatment level), the model finds that the guidance was appropriate for ~90% of patients. For ~10% of patients, smaller statin doses achieved better cholesterol lowering than the higher doses recommended by NICE guidance.

Conclusions
Machine learning can identify patient subgroups for whom smaller statin doses that deviate from NICE guidance may be a viable therapeutic option. We conjecture that better cholesterol lowering with smaller statin doses reflects better therapy adherence due to reduced side-effects. This hypothesis is testable in prospective studies.