Apo-calypse now? Apolipoprotein profiling to reduce residual cardiovascular disease

Reijnders, E.

APO-CALYPSE NOW?

Apolipoprotein Profiling to Reduce Residual Cardiovascular Disease

Esther Reijnders

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Apo-calypse Now: Apolipoprotein Profiling to Reduce Residual Cardiovascular Disease

E. Reijnders

PhD thesis, Leiden University Medical Center, 2025

Cover image:	*Under the Wave off Kanagawa* by Katsushika Hokusa
Layout & cover design:	Parntawan Kidtam | www.ridderprint.nl
Printing:	Ridderprint | www.ridderprint.nl
ISBN:	978-94-6522-603-3

Apo-calypse Now?
Apolipoprotein Profiling to Reduce Residual Cardiovascular Disease

Proefschrift

ter verkrijging van

de graad van doctor aan de Universiteit Leiden,

op gezag van rector magnificus prof.dr.ir. H. Bijl,

volgens besluit van het college voor promoties

te verdedigen op donderdag 30 oktober 2025

klokke 11.30 uur

door

Esther Reijnders

geboren te Bergen op Zoom

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Mille periculis supersum

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OUTLINE OF THIS THESIS

This thesis explores the use of an apolipoprotein panel, comprising Apo(a), ApoA-I, ApoA-II, ApoA-IV, ApoB, ApoC-I, ApoC-II, ApoC-III, and ApoE, as well as the ApoE phenotype, to enhance cardiovascular risk prediction beyond the conventional lipid panel. Apolipoproteins, as key proteins in lipid metabolism, are promising candidates for refining cardiovascular risk assessment.

The journey began with identifying an unmet clinical need, which is a crucial first step in developing and implementing any new diagnostic test. In this case, the focus was on addressing residual cardiovascular risk, risk that persists despite optimal management of low-density lipoprotein cholesterol (LDL-C). **Chapter 1** describes this residual cardiovascular risk and the multitude of risk factors contributing to this risk beyond LDL-C.

Moving forward to a more defined strategy, **Chapter 2** presents the rationale for selecting the nine apolipoproteins, the reason to use liquid chromatography-multiple reaction monitoring-mass spectrometry (LC-MRM-MS) as the measurement technique, and the need to measure apolipoproteins as a comprehensive panel rather than as individual markers.

Chapter 3 provides a brief summary of the MS-based multiplex apolipoprotein test, including the relevant peptides and the applied pre-analytical procedures.

Following the test evaluation framework established by the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM), the analytical performance of the apolipoprotein panel was validated prior to the start of this thesis. The next step involved assessing its clinical performance and clinical effectiveness. To achieve this, samples from clinical studies needed to be analyzed. To ensure high quality data, **Chapter 4** outlines a comprehensive quality assurance approach for measuring large volume of clinical samples with the apolipoprotein multiplex test. With this foundation in place, the path was clear to evaluate the clinical performance and establish the clinical effectiveness of the apolipoprotein panel in improving cardiovascular risk prediction.

In **Chapter 5,** the clinical performance of the apolipoprotein panel was assessed within the NEO study, a Dutch cohort of middle-aged, predominantly overweight, and predominantly white individuals without pre-existing cardiovascular disease. Additionally, reference intervals for all nine apolipoproteins were calculated based on a subpopulation representative of the general Dutch population.

Building on these findings from a primary prevention context, **Chapter 6** extends the evaluation to a secondary prevention setting using data from the ODYSSEY OUTCOMES trial. Here, the clinical performance and effectiveness of the apolipoprotein panel were further investigated, including its potential to enhance risk prediction and therapeutic guidance in patients receiving the PCSK9 inhibitor alirocumab.

Quantification of lipoprotein(a) (Lp(a)) has proven to be difficult due to the heterogenous nature of Apo(a), challenging immunoassay-based tests. In **Chapter 7** we compared the prognostic and predictive performance of two immunoassay-based tests and the multiplex LC-MRM-MS test for Lp(a) in relation to major adverse cardiovascular events (MACE).

Chapter 8 reflects on the thesis and explores how the apolipoprotein panel test could be integrated into the current clinical care pathway. It discusses its potential to enable precision diagnostics and align with the principles of P5 medicine.