Targeting the vessel wall in cardiovascular prevention
Meuwese, M.C.

Citation for published version (APA):
In part 3, I describe the one of last stages of research before application in the clinic, a randomized controlled trial (RCT). On the one hand this part shows the failure of the novel class of drugs intended for cardiovascular prevention, i.e. acyl coenzyme A:cholesterol acyl transferase (ACAT) inhibitors aimed at reducing foam cell formation in the vessel wall. On the other hand it shows the power of surrogate markers, such as carotid intima-media thickness (IMT) measurements, in assessing the effect of therapy on cardiovascular risk.
INTRODUCTION

Despite current treatment modalities, cardiovascular disease is still the leading cause of death in the world. Many new approaches to prevent cardiovascular disease and treat its risk factors, such as dyslipidemia and diabetes, have been developed in recent years. Unfortunately, many stranded, at animal level, in clinical trials (for example MTP inhibitors, torcetrapib), or even after introduction to the market (e.g. thiazolidiones) (1-3).

These recent disappointments may be frustrating, but also illustrate the importance of every stage in medical research, from generating a sound hypothesis, initial testing in the laboratory and in animal models, to conducting human trials to assess safety and efficacy. To use the words of Steve Nissen: “There is only one way: through good science”. In atherosclerosis research, human imaging studies are particularly of value. They provide an impression of drug efficacy, long before large scale morbidity and mortality trials are conducted and their results are available (4).

ACAT inhibitors were developed the past decades as a new way to reduce atherosclerosis. In theory, their mechanism of action is dual. Inhibition of ACAT1 could prevent the transformation of macrophages into foam cells in the vessel wall. This would slow the progression of atherosclerosis and prevent the development of vulnerable plaque. In addition, inhibition of ACAT2 could decrease serum lipid levels by reducing the synthesis of lipoproteins. (5)

HYPOTHESIS

Inhibition of ACAT was expected to slow the progression of atherosclerosis as assessed by IMT imaging.

OUTLINE

Chapter 13 describes the rise and fall of ACAT inhibitors. Next, we review the value of IMT as surrogate marker for cardiovascular disease (chapter 14). Finally, in chapter 15, we present the results of the CAPTIVATE study. This study was designed to evaluate the effect of the ACAT inhibitor pactimibe on atherosclerosis progression as assessed by IMT measurements in patients with familial hypercholesterolemia.
REFERENCES