Prologue

This manuscript describes an attempt of elucidating only a minute aspect of a complex problem, known as coronary artery disease (CAD). With an estimated 8 million deaths per year, CAD remains among the leading causes of premature death in the world, despite the fact that prevention, lifestyle interventions, pharmacologic strategies and revascularization have led to a decline in mortality rates over the past decades. Nevertheless, the fact that the number of life years lost to premature deaths is increasing in low- and middle-income regions is alarming.[1]

Patients with a formal diagnosis of CAD are at the scope of this thesis. For these patients, epidemiologists have been able to successfully create prediction models that aim to estimate the risk of death or myocardial infarction within a set timeframe. These models depend on the presence and recognition of traditional risk factors (such as hypertension, diabetes, smoking etc.) and cardiovascular history complemented by biometric factors. However, traditional cardiovascular risk factors are absent in a significant part of the population that nevertheless will develop CAD and its sequelae. In contrast, the prevalence of traditional risk factors is also high among the fraction of the population that will never endure a major adverse cardiovascular event (MACE) [2].

According to the key philosophy behind existing risk prediction models, the individual patient is considered to be a member of a group that is exposed to a certain (low-intermediate-high) constant risk over time, whereas the incidence of acute cardiovascular events is considered a random process, with event probabilities directly related to that group risk. Consequently, cardiovascular risk models usually predict reasonably well on a group level, but only poorly outline the course of individuals. [2] In addition, current risk prediction models do not account for the dynamic nature of the coronary pathophysiology. Individual patients with CAD actually do not have constant risks over time. Long periods of stability, with minimal plaque progression and low risk of cardiovascular events, are alternated by periods of increased plaque instability and rapid plaque progression, during which the risk of sudden plaque disruption and thrombotic coronary occlusion increases. [2]

Against this background, the common thread throughout parts 1 to 3 of this thesis is the search for improvement of risk prediction in patients with known CAD, i.e. more precise identification of those vulnerable for suffering a coronary event in the future.

Part 1, *"**Vulnerable Blood**"*, focusses on the additional value of several serum biomarkers for the prediction of MACE on a relatively long term (4 to 10 years of follow-up). These markers are traditionally measured once at the start of follow-up and hence assumed to reflect a constant cardiovascular risk, in a similar way as traditional risk models incorporate clinical risk factors.

Part 2, *"**Vulnerable Period**"*, focusses on serum biomarkers as well, but here the train of thought is more in line with the dynamics of coronary pathophysiology, i.e. that the risk of MACE within an individual patient is not constant, but variable over time. Hence, repeated biomarker measurements are explored in the BIOMarker study to identify the Acute risk of a Coronary Syndrome (BIOMArCS), in order to evaluate whether fluctuations in biomarker levels can predict the risk of an imminent MACE within the days to weeks to come.

In ***Part 3***, *"**Vulnerable Plaque**"*, the centre of interest is around invasive coronary imaging, including coronary angiography, intravascular ultrasound (IVUS) and near-infrared spectroscopy (NIRS), for the prediction of MACE, as well as cross-sectional analyses evaluating the relation between these imaging techniques and serum biomarkers.

Accurate risk prediction is important to understand future risks of CAD patients, but clearly prediction alone will not alter their outcome. For that purpose, intervention studies are required in those deemed at high risk. Such studies, often combined with the search for those patient subsets to derive most benefit from the interventions, are described in ***Part 4***, *"**Intervention Studies**"*.

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