Chapter 1.

General Introduction And Outline Of This Thesis

Published in part as:

PET And SPECT Imaging Of Apoptosis In Vulnerable Atherosclerotic Plaques With Radiolabeled Annexin A5

Eduard M. Laufer\textsuperscript{1,2}, Mark H.M. Winkens\textsuperscript{1,2}, Maarten F. Corsten\textsuperscript{1,2}, Chris P.M. Reutelingsperger\textsuperscript{1,2}, Jagat Narula\textsuperscript{3} and Leonard Hofstra\textsuperscript{1,2}

1. Department of Cardiology, Maastricht University Medical center, Maastricht
2. Cardiovascular research Institute Maastricht, Maastricht The Netherlands
3. Department of Cardiology, University of California Irvine,

Coronary artery disease, a global burden

What is facing us, is that due to the aging population and the epidemic proportions of obesity and diabetes type II, an increase in coronary artery disease is expected. This means, in the current situation, healthcare is faced with spiralling costs, which do not necessarily translate in increases in Healthy Life Years. For instance, the Netherlands invest more than 13% of GDP in Health Care, but sees a lower than average return of Health Life Years compared to other European countries.

Despite numerous effective developments in medicine, cardiovascular disease is still a major cause of death in the Western world. Moreover, in emerging economies such as China or India, a rapid rise of incidence of cardiovascular disease has been predicted. There is consequent growing demand for novel tools to detect disease in a very early or even pre-disease state before it reaches stages of irreversible injury.

Atherosclerotic plaques are the net result of a complex interplay between vascular cholesterol deposition, inflammatory activity and extracellular matrix formation. The result is luminal narrowing of arteries, which may ultimately lead to compromised blood flow to essential body organs, most notoriously to the heart. Most of the cardiovascular events that are caused by atherosclerosis, such as acute myocardial infarction or stroke, are the result of a transition of so-called stable atherosclerotic plaques to vulnerable plaques that are prone to rupture. The direct consequence of atherosclerotic plaque disruption and endothelial erosion is exposure of thrombogenic constituents to the blood, leading to instant local thrombus formation. The formation of this localized thrombus may ultimately result in sudden obstruction of blood flow and consequent infarction of tissue distal to the lesion.

How to predict risk?

The 10-year risk of myocardial infarction can be estimated based on large prospective clinical studies using simple questionnaires and lipid profiles. By using relatively straightforward clinical risk profiling methods applied to large cohorts, such as the Framingham risk score, Procam or SCORE risk scores, patients with a high cardiovascular risk can be identified. However, clinical risk profiling cannot help predict which individual patient will actually be affected by myocardial infarction. In addition, it is not clear when exactly the acute myocardial infarction will occur. Diagnostic tests that could
accurately predict which patients are at imminent risk could potentially save thousands of unnecessary worldwide cardiovascular deaths. However, such a technology is currently lacking. The clinical need to identify the patient at imminent risk of cardiovascular events has propelled the development of detection methods like innovative serum and imaging biomarkers, which are currently being tested for their clinical value and relevance.

Biomarker detection: better prediction?

Increasing involvement of molecular biologists in cardiovascular research has helped improve our insights in how to improve prediction of cardiovascular events. But despite increasing insights the translation of basic science findings into relevant, affordable and widely available clinical diagnostics has been lacking to help identify the patient at imminent risk. One of the success stories in this translation to clinical practice has been the development of high-sensitivity-C-reactive-protein (hs-CRP) to trace patients at instant cardiovascular risk. The idea is based on the fact that atherosclerotic plaque rupture is associated with inflammatory processes in this unstable plaque. However, despite this biological association, clinical studies have shown that hs-CRP is of limited practical use in predicting acute vascular events. Recently, however, hs-CRP is successfully deployed to discriminate patients that could benefit from anti-inflammatory therapy and lower the risk at acute coronary events.

Role of imaging

Another approach to improve cardiovascular risk prediction is the use of imaging. Currently available cardiovascular imaging techniques, such as cardiac ultrasound, Single photon emission computed tomography (SPECT), positron emission tomographic computed tomography, invasive coronary angiography (CAG), magnetic resonance imaging and cardiac computed tomographic angiography (CCTA) are superb imaging modalities which are able to assess left ventricular function, visualize the burden of atherosclerosis and detect obstructive coronary artery disease and even high risk coronary plaques causing acute coronary syndromes. Despite their clinical usefulness for showing anatomy, and their continuous improvement in the last years, these imaging tools are less capable to reveal molecular changes in
cardiovascular disease. As a result, we still do not know much when plaque destabilize over time and how they behave over time. Vulnerable plaques are characterized by a thin fibrous cap, a large necrotic core, positive remodelling, and the presence of inflammatory cells. Furthermore, coronary artery plaque erosions are responsible for thrombotic coronary events and seem to be associated with positive coronary plaque remodelling. Due to the incapability to detect such molecular and cellular changes, the predictive value of current imaging technologies is limited in the prediction of plaque rupture. For example, CCTA and CAG are excellent tools to visualize lumen reduction and plaque characteristics. However, which of the detected atherosclerotic plaques have the characteristics of a vulnerable plaque and are prone to rupture cannot be inferred.

Better integration of care

A neglected factor in optimizing care and better identification in patients at risk for coronary events is to improve integration of care. In the previous sections, we discussed the development of novel biomarkers and imaging tools to better define the patient at risk of coronary artery events. This can be classified as biological or technological improvements. However, seamless connection of the different layers in healthcare may be as important as technological advances.

As stated previously in the introduction, our healthcare system will be faced by spiralling costs due to the aging population and unhealthy lifestyle. Better alignment and integration of public health and healthcare may be of help to address these challenges. A critical factor in health care quality and delivery is the disconnection between traditional health care institutions and public health. In addition, there is insufficient collaboration between primary and secondary health care institutions, resulting in suboptimal patient care and value.

In the Netherlands we have started to address these challenges, with the aim to connect different layers of health care and aspire full integration of cardiovascular care. For this purpose, we designed CRISP, for Cardiovascular Research Innovation and Sustainability Platform. CRISP started as a joint project between Cardiology Centre Utrecht and a foundation of 13 general practitioners (GP) delivering primary care to 35,000 citizens in the city of Utrecht (“Utrecht Oost Gezond”). CRISP restructures and integrates cardiovascular care to avoid unnecessary use of expensive health care to low
risk individuals and identifies high risk individuals and provides them with timely measures to prevent cardiac disaster. A schematic representation is given below.

Figure 1. The colours red, orange and green represent the patients at respectively high, intermediate and low risk for coronary disease. The percentages are estimated.

**First step: online heart risk and lifestyle test.** CRISP starts with an on-line heart risk and lifestyle test which is provided through the GP’s website, offered to all inhabitants of Utrecht-Oost. Either healthy lifestyle information to maintain a low risk given (in case of a green outcome meaning low heart risk), or an advice to visit the GP’s office for further evaluation (in case of orange intermediate or red high risk). A critical factor within CRISP is that the GP nurse also receives the online test outcome thereby establishing an essential connection between public health and health care.
Second step: GP nurse. Next, a GP nurse will refine risk profiling using lipid profile, blood pressure and glucose measurements in orange and red cases. Low risk cases are send home with healthy lifestyle advice (exercise, stress reduction and diet).

Third step: GP. Individuals with a persistent orange or red outcome will visit the GP once. The GP will initiate appropriate medical care and lifestyle advice to treat blood pressure, high cholesterol levels or diabetes with follow up of the GP nurse.

Fourth step: Cardiology Centre. In case of cardiac complaints or very high risk, the GP will refer the patient to the Cardiology Centre within one day. If the outcome of exercise testing, echocardiogram and carotid imaging is negative, the patient will be referred back to the GP.

Fifth step: CT imaging. In positive cases medical treatment is initiated, and the patient may be referred for step wise CT coronary imaging starting with a Ca scan and followed by contrast CT only if Calciumscore is higher than 0. In case of a critical CT outcome, the patient is referred for percutaneous intervention.

Sustainable care at low cost. The implementation of the doctor led initiative CRISP aims to reduces “waste”, and to optimize timely delivery of care. In addition, CRISP links public health and general health care, which results in better alignment of resources and improved patient value. The CRISP project has resulted in better alignment of care and integration of cardiovascular care at the GP level and Cardiology Centra Nederland. However, in different parts of the CRISP cycle added value through better diagnostics and risk prediction should be possible. For instance, in the public health domain awareness and education could be optimised in close collaboration with GP delivery care. In addition, a better prediction of coronary atherosclerosis through detection of serum biomarkers would help to avoid unnecessary imaging studies in some patients, while it would help to expedite care in high risk patients.

Scope of this thesis

In the current thesis, we aimed to optimize several steps in the CRISP circle. We sought to improve the several elements of the total integrated care cycle rather than focus on only one particular subset of the circle.

In Chapter 2, the effect of low cost, fast and simple mass screening with a big role of digital communication, in a long-term 10-year follow-up study, is examined in voluntary participants. The study is part of the Heart Attack
Prevention Program for You (HAPPY). The parameters needed to calculate the Procam score were filled in online and the participants visited a “health fair” to measure their weight, length, waist-circumference and draw blood for lipid levels measurement. The personal Procam score was calculated and communicated by e-mail. Monthly computer tailored advise was given by e-mail for 3 months. After 3 months, the measurements were repeated and compared to the index measurements. Lastly, 10 years after the screening, participants are asked by mail whether they suffered myocardial infarction or not to test the Procam accuracy. This program was executed in close collaboration with general practitioners.

Is a low cost, fast and simple mass screening using digital communication feasible? What are the effects of the digital communication on the risks scores 3 months after the first screening?

In chapter 3 and 4, the potential impact of the next generation of high sensitivity troponine T (hs-TnT) reagents is studied. Troponin is part of the sarcomere. In resting state, tropomyosin covers the myosin-binding sites which are present on actin filaments. Troponins are crucial in positioning tropomyosin. When calcium binds to troponin, these binding sites are uncovered enabling myosin to bind to the actin binding sites. Subsequently, ATP-hydrolysis, the actin is pulled by the myosin filament and the contraction of the cardiomyocyte is effected. Cardiac troponin is highly specific for the cardiomyocyte. With the former 4th generation of assays, troponin T was not measurable in normal conditions (no myocardial infarction) in the peripheral blood outside the cardiomyocytes. The 5th generation hs-TnT assays is able to measure very low levels of troponin. The relation between the extent of coronary disease and prognostic value of hs-TnT is investigated in chapter 3 and 4.

Is troponin an independent biomarker of stable and instable coronary disease?

In chapter 5 the role of promising inflammation biomarkers in coronary artery disease and the prediction of cardiac events are presented in a 9-year follow-up study. Inflammation is an important mediator in the progression of coronary atherosclerosis and the transition to vulnerable plaque phenotype. We studied the association between inflammation biomarkers and both coronary plaque burden and cardiac events.

Are Annexin A5, Elastase and Myeloperoxidase useful biomarkers in clinical detection of coronary disease and future coronary events?

Chapter 6 handles the relation between vitamin K antagonist use and coronary plaque formation in both animal models as in patients. Growing
evidence shows progression of coronary calcium in vitamin K antagonist use. Matrix Gla-protein is a vitamin K-dependent protein and inhibits calcification in cartilage and arteries. We investigated the role and mechanism of vitamin K antagonists in the calcium metabolism and the effect on coronary atherosclerosis.

Is vitamin K antagonists use correlated to acceleration of coronary calcification?

Chapter 7 reviews several advanced non-invasive imaging techniques for detection of the patient, vulnerable to myocardial infarction. The need to identify the vulnerable plaque might be met by development of specific probes and these advanced imaging tools in the future.

What can molecular imaging bring us now and in the future in the detection of coronary disease?

Finally, the findings of the original research papers are summarized and discussed in Chapter 8.

The figure (2) below represents an overview of the thesis, each element corresponds to a chapter of the thesis.

Figure 2. The colours red, orange and green represent the patients at respectively high, intermediate and low risk for coronary disease.
References:


Chapter 1 | General Introduction and Outline of This Thesis