Optimization of secondary prevention and risk stratification in patients with coronary heart disease

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Chapter 9.

Summary, conclusions and future perspectives

Samenvatting, conclusies en toekomstperspectieven

Summary

The general introduction of this thesis provided an overview of the development of atherosclerosis, treatment and risk stratification in patients with ST-elevation myocardial infarction (STEMI). Despite the impressive improvement that has been achieved in the field of cardiovascular disease it still is of great importance to identify patients at risk for (recurrent) adverse event. The objective of this thesis was to improve risk stratification and identify high risk populations in STEMI patients. Secondly this thesis sought to further optimize the treatment in patients with STEMI or cardiovascular disease.

Chapter 2 was an update on the pathophysiology of atherosclerotic disease and related current and possible future medical interventions with a focus on low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides (TG) and lipoprotein(a) (Lp(a)). Lowering LDL-C by statin therapy remains, to date, the cornerstone for the medical prevention and treatment of atherosclerotic disease. Ezetimibe should be considered in a sub high risk population who do not obtain the desired LDL-c level with intensive statin treatment. Bile acid sequestrants, fibrates and niacin are not recommended. Upcoming PCSK-9 inhibitors are new potent agents for dyslipoproteinaemia. HDL-C modulation through cholesteryl ester transfer protein (CETP) inhibition and apo A-I mimetics did not yet provide evidence for better cardiovascular (CV) outcome. New classes of molecules targeting ANGPTL3 and Lp(a) have shown promising efficacy and good short-term safety profiles in early phase trials and these result warrant further development.

Chapter 3 assessed the long-term prognosis of STEMI patients referred to the general practitioner (GP) after treatment according to the 1-year institutional MISSION! MI protocol. In total, 922 patients were referred to the GP. Median follow-up was 4.55 year. At baseline (at the end of the 1-year MISSON! MI protocol) the mean age was 61 years and 75% was male. After follow-up 93% was still alive and 80% remained event-free. Patient at higher risk for mortality or adverse events were patients with higher age, smokers, history of a malignancy or stroke, not using an ACE-i/AT2-antagonist or aspirin, an impaired left ventricular ejection fraction (LVEF), a mitral regurgitation (MR) grade ≥ 2 and multivessel disease during pPCI. Since there are no recommendations in international guidelines for the appropriate duration of follow-up in the outpatient clinic after a STEMI, this 1-year period might be applied in future guidelines. However, patients with an impaired LVEF and patient with an MR grade ≥ 2 should be considered as higher risk patients and should stay in the outpatient clinic of a cardiologist.

Chapter 4 studied the value of extensive serum apolipoprotein (apo) profiling and the risk of adverse events in patients with STEMI in a case-control design study. It is suggested that the measurement of functional and structural protein

components of lipoproteins, *i.e.* apolipoprotein (apos) has additional value for coronary artery disease (CAD) risk assessment. In total, 220 STEMI patients and 299 control subjects were identified. Overall, the STEMI group had a lipid profile consistent with an increased CV risk. ApoA1 was significantly lower in the STEMI group than in the control group and apoB was significantly higher in the STEMI group than in the control group. High remnant cholesterol, low ApoA1, high ApoB and high apoB/apoA1 ratios were strongly associated with STEMI risk. The VLDL-associated apos gave conflicting results. At discharge 100% of the STEMI patients were on statin therapy. In patients with STEMI 83 events were observed after a mean follow-up of almost 9 years. For each baseline lipid and apo species the hazard ratio for MACE was calculated after adjustment for age, gender and statin use. Neither conventional lipid level nor apo levels were associated with a recurrent event in the STEMI group. This could be explained since 100% of the patient were on statin therapy which significantly reduced the lipid concentrations. This, together with the limited number of recurrent events could explain why no association was found between apos or lipid concentrations and recurrent events.

Chapter 5 was performed to investigate the additive prognostic value of growth-differentiation factor (GDF-15) levels in patients with STEMI with 10-year mortality on top of clinical characteristics and known cardiac biomarkers. In 290 STEMI patients baseline GDF-15 samples were measured. Mean age was 59 years. Stratified by median GDF-15 and median NTproBNP levels, Kaplan-Meier curves showed significantly better survival for patients with GDF-15 and NTproBNP levels below the median than for patients with GDF-15 and NTproBNP levels above the median. Furthermore, an incremental value of GDF-15 was found, as compared with a model with clinical important variables and NTproBNP. So, the combination of these biomarkers seems to identify an interesting group of high risk patients. In the group of patients with both GDF-15 and NTproBNP levels below the median, only 3 patients (3.8%) died within 10 years compared to 22 (27.8%) in the group with both GDF-15 and NTproBNP levels above the median.

Chapter 6 aimed to determine how rapidly high-sensitivity troponin–I (hs-cTnI) levels are lowered by statin therapy in patients with stable cardiovascular disease. A total of 80 patients were included in this present official and prospective sub study of the RADAR (Rosuvastatin and Atorvastatin in different Dosages And Reverse cholesterol transport) study to assess serum hs-cTnI. In the RADAR study, patients with stable CVD entered a 6-week dietary run-in phase. Subsequently, they were randomised to receive either ATOR 20mg or ROSU 10mg. On the following visits, at 6 and 12 weeks the doses were, by protocol, forced up-titrated to 40 mg ATOR or 20mg ROSU (at 6 weeks) and 80 mg ATOR or 40 mg ROSU (at 12 weeks). The study in this thesis, shows that Hs-cTnI decreased significantly during statin therapy, which was independent of decreases of LDL-c concentrations. Interestingly this suggests a rapid benefit of

statin treatment on ongoing subclinical myocardial damage.

Chapter 7 evaluated the association of baseline LDL-c level with infarct size in patients with STEMI treated with a pPCI. In this study, 2248 patients were included with a mean age of 61.8 years. LDL-c values were positively associated with infarct size which was expressed with peak creatine kinase (CK) level. Adjusted for confounders LDL-c levels were independently associated with peak CK level. Due to improvements of diagnosis, therapy and care, mortality rates of STEMI patients are reduced at the expense of expanding number of STEMI patients with heart failure. This makes it essential to understand what factors are associated with infarct size, particularly if these factors are potentially modifiable, as this could lead to the earlier detection and development of advanced therapies.
Chapter 8 investigated the feasibility and efficacy of a novel pre-hospital triage protocol for use in the cardiac emergency department. Eligibility for admission at the cardiac emergency department was based upon the novel dedicated pre-hospital triage protocol. Patients admitted to the cardiac emergency department were classified into three groups based upon presenting symptoms: chest pain, palpitations or cardiac device related problems. Patients presenting with other symptoms at the cardiac emergency department were defined as incorrect triage. Of the 1107 included patients, the incorrect triage rate was 3.2%, with the most common presenting symptoms in the incorrect triaged patients being collapse (n=15; 43%) and dyspnoea (n=8; 23%). After evaluation at the cardiac emergency department the majority of patients were discharged home (n=920; 86%). A total of 34 patients were admitted to the cardiac care unit (3%), 110 to the cardiology ward (10%) and only 8 were admitted to a non-cardiac ward (1%). This demonstrates that using a dedicated pre-hospital triage protocol is a feasible and effective tool to select patients for admission at the cardiac emergency department.

Conclusions and future perspectives

The last decades risk stratification, treatment and prognosis in STEMI patients have dramatically improved. However still a substantial amount of death occurs with a wide variability between patients. The first part of this thesis identified patients at low risk for recurrent events or death after STEMI. It was observed that asymptomatic patients with a LVEF>45% after one year can safely be referred to the GP with mortality rates after STEMI that come close to the rate in the general population. Furthermore, patients were identified who were at higher risk for recurrent events. For example, patients with a MR grade ≥ 2 should be considered as higher risk patients and should stay in the outpatient clinic of a cardiologist**.** Further research is needed to explore and identify all patient eligible for referral to the GP after treatment and the possibilities to refer stable patient with STEMI within one year to the GP should be discovered.

The second part of this thesis focused to identify high-risk subpopulations to improve risk stratification and made a start towards more patient tailored care. It was found that extensive lipid and apo profiling can significantly contribute to predict STEMI or major recurrent events. Mainly, apoA1, apoB and apoB/A1 ratio and remnant cholesterol were strongly associated with risk of STEMI and apoB/A1 ratio being superior to LDLc and non-HDLc. Despite current standards of care aimed at achieving targets for LDLc and other traditional risk factors, STEMI patients remain at high risk of new cardiovascular events. Valuable effort should therefore be made to further reduce residual cardiovascular risk by using additional more discriminating and more refined treatments targets like apoB and apoB/apoA1 ratio. Furthermore, novel biomarkers were identified to improve risk stratification and select high risk sub-populations. GDF-15, a more general marker for disease severity in STEMI patient demonstrated to have an additional prognostic value beyond identified risk factors and other cardiac biomarkers such as cTn and NT-proBNP. Currently it is unclear how GDF-15 levels can be lowered and whether lowering these levels result in an improved outcome. Therefore, further research regarding the pathophysiological mechanisms and the influence of common and novel medical therapies on GDF-15 levels should be explored. Whether more aggressive medical therapy by for example PCSK-9 inhibitors has beneficial effects on GDF-15 is worth investigating. Another way to influence GDF-15 levels may be by anti-inflammatory therapy. It would be of interest to explore whether GDF-15 levels may act as biomarker-guided therapy to evaluate the effect of anti-inflammatory therapy.

Lastly, the third part of this thesis showed that a dedicated pre-hospital triage protocol is a feasible and effective tool to select patients for admission at the cardiac emergency department. Overcrowding is a major public health problem and this thesis shows that the introduction of dedicated cardiac emergency departments can potentially reduce the caseload of the general emergency department. Further studies are needed to evaluate whether pre-hospital triage protocol can also help to reduce the use of medical facilities, decrease admission times and lower health care expenditures.