Statin treatment in type 2 diabetes patients

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General introduction

The prevalence of type 2 diabetes is increasing in the Netherlands as in many countries worldwide [1]. In 2011, more than 830,000 patients were diagnosed with diabetes in the Netherlands, 90% of these patients with type 2 diabetes [2]. An increasing number of patients with obesity or physical inactivity, early diagnosis of type 2 diabetes, and aging of the population are among the main reasons for this increase in prevalence rate [2]. The high prevalence of diabetes reflects a substantial disease burden with considerable healthcare costs. The total Dutch healthcare costs related to diabetes were estimated at 1.7 billion euro's for the year 2011 [3]. An important part of diabetes-related healthcare costs is caused by costs due to micro- and macro-vascular complications of diabetes [4-6].

Cardiovascular complications of diabetes

Patients with type 2 diabetes are more likely to develop cardio- and cerebrovascular disease than individuals without diabetes. It has been estimated that patients with diabetes without a prior myocardial infarction have a risk for myocardial infarction as high as patients without diabetes, but with a history of myocardial infarction [7]. In addition, mortality rates following a myocardial infarction are higher among patients with diabetes [8]. Around 60% of patients with diabetes die from any type of cardiovascular disease or stroke [9]. Therefore, the control of cardiovascular risk factors, including dyslipidaemia, is essential.

Control of dyslipidaemia with statin treatment

HMG coenzyme-A reductase inhibitors (statins) are the most important drug class for controlling dyslipidaemia. HMG-CoA reductase catalyses the conversion of HMG-CoA to mevalonate, which is the rate-limiting step in the cholesterol synthesis. Competitive inhibition of this enzyme by statins decreases hepatocyte cholesterol synthesis and stimulates expression of LDL-cholesterol receptors [10]. This results in a reduction in the intracellular cholesterol concentration which causes an increased extraction of LDL-cholesterol from the blood and therefore decreases circulating LDL-cholesterol concentrations [11]. Statins are also linked to various pleiotropic effects that are independent of their effects on lipids and associated with a variety of improved outcomes [12].

In 2014, five different statins were available on the Dutch market with over 1,900,000 users in the Netherlands [13]. The extent to which the statin lowers LDL-cholesterol is dependent on the potency and dosing (potency: rosuvastatin> atorvastatin> simvastatin> pravastatin> fluvastatin) [14]. In general, doubling the statin dose has been associated with an additional 7% reduction in LDL-cholesterol from baseline [15]. Meta-analyses have reported a reduced risk for cardiovascular events with statin treatment in both primary and secondary prevention populations [16,17]. Besides the reductions in

cholesterol levels and cardiovascular events, adverse events have been associated with statin treatment. Muscle toxicity and effects on liver enzymes are well acknowledged, the risk is, however, low [18]. Rhabdomyolysis is a severe, but rare, form of muscle toxicity involving muscle breakdown which can cause renal failure and can be fatal [18]. Although the risk for adverse events is low, for patients with a low cardiovascular risk they could possibly outweigh the benefits of treatment.

Statin treatment recommendations

The need for statin treatment for secondary prevention of cardiovascular events is widely recognized. Since 2006, Dutch guidelines recommend statin treatment for both primary and secondary prevention for almost all diabetes patients [19,20]. Standard-dose statin treatment (simvastatin 40 mg) is recommended for all diabetes patients with a history of cardiovascular disease [19,20]. The use of statin treatment for primary prevention is, however, more controversial. The Cochrane Collaboration, for example, emphasized in 2011 that caution should be taken in prescribing statins to diabetes patients without risk-elevating medical conditions [17].

Treatment recommendations in the Dutch guidelines are based on individual estimated cardiovascular risk scores. Statin treatment is recommended for all patients with a 10-year cardiovascular risk of ≥10% and an LDL-cholesterol level >2.5 mmol/l. This acknowledges that for patients with low estimated risks or with low LDL-cholesterol levels statin treatment might not be cost-effective nor improve patient quality of life [17]. When following the current guideline an increasing number of diabetes patients might not be eligible for statin treatment as type 2 diabetes is nowadays diagnosed earlier and at a younger age, with lower cardiovascular risk at diabetes diagnosis as a result.

Cost-effectiveness of statin treatment

The recommendation in the Dutch guidelines to start statin treatment with simvastatin 40 mg is based upon cost-effectiveness analyses [19]. In 2003, simvastatin was the first generic statin that entered the Dutch market resulting in a large reduction in the simvastatin price. This price reduction had a positive effect on cost-effectiveness of simvastatin treatment and allowed broader prescribing of simvastatin.

Cost-effectiveness calculations are usually based on efficacy data from clinical trials. Clinical trial populations often do not reflect the population treated in clinical practice. Also, in clinical trials patients are treated under well controlled conditions, which is not the case in clinical practice [21]. This probably affects cost-effectiveness, and may lead to overestimations.

Treatment non-response in clinical practice

Observational studies have shown that in clinical practice cholesterol targets are not reached by at least a third of patients [22,23]. This lack of treatment response could be due to being prescribed low-dose treatment [22,24], lack of treatment intensification [25,26,27] and/or non-adherence to treatment [28,29].

Being prescribed a dose lower than recommended is a problem in clinical practice. Patients treated with a low dose are more likely not to reach their LDL-cholesterol target [22]. In 2006, 20 mg was the most often prescribed dose of simvastatin [22]. Although the treatment dose has been increasing over the years, patients were on average treated with a dose lower than recommended in the Dutch guideline in 2006 [19,22,24].

Furthermore, it has been shown that at least a third of the patients that are not reaching their LDL-cholesterol target do not receive any treatment modification [25,26,27]. This could be related to non-adherence, as suspicion of non-adherence to treatment could be reason for the physician not to intensify treatment. However, the ability of physicians to recognize non-adherence is poor [30]. There is some evidence of possible redundant treatment intensification in non-adherent patients [31], but also lack of treatment intensification in adherent patients [26]. More insight in prescribing and adherence patterns is needed to improve treatment response.

Adherence to treatment

Non-adherence to statin treatment is an important problem, which is associated with less decrease in LDL-cholesterol [28,29] and with a higher risk for cardiovascular events and all-cause mortality [32]. The World Health Organization (WHO) has adopted the following definition of adherence to long-term treatment: *The extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider* [33]. Adherence can be measured using prescription data as the Proportion of Days Covered (PDC) which expresses the proportion of days for which a patient has received medication in the study period [34]. Patients are often categorized as adherent or non-adherent for which an arbitrary cut-off point of 80% PDC is commonly used [35]. It has been reported that only 50% of the patients remains adherent, that is PDC >80%, during the first years of treatment [36,37]. Also discontinuation rates of statin treatment may be high during the first years of treatment [38]. Adherence to and discontinuation of treatment is influenced by patient's preferences. Non-adherence and discontinuation appear to be more common in patients that are female, have no cardiovascular history, have experienced adverse effects and have a lower socioeconomic status or education [39,40,41]. Better insight in patient's preferences for lipid-lowering drugs according to patient characteristics could be useful

for motivating patients to continue using statin treatment and thereby improve health and economic benefits.

Research aims and outline of the thesis

Type 2 diabetes patients have a higher risk for developing cardiovascular and cerebrovascular disease therefore statins are recommended for almost all diabetes patients. This thesis will focus on statin treatment in type 2 diabetes patients. **Part I** is about the effects of statin treatment on LDL-cholesterol and cardiovascular and cerebrovascular outcomes and about cost-effectiveness estimates, using clinical trial and observational data from routine medical practice. It provides updates on meta-analyses and precise effect estimates for statin treatment in diabetes patients. For clinical decision making and cost-effectiveness analysis, it is important to have such precise estimates. Moreover, the impact of real-world adherence and dosing of statin treatment on the outcomes are assessed. These factors are expected to affect the cost-effectiveness of statin treatment in daily practice. **Part II** elaborates further on both patient-related factors (e.g. adherence to treatment, patient's preferences) and physician-related factors (e.g. treatment dosing, and modifications) that affect outcomes of statin treatment.

Part I. Effects and cost-effectiveness of statin treatment

The aims of the first part are to:

- determine precise effect estimates of statins for primary and secondary prevention of cardiovascular events in diabetes patients;
- assess the effect of dosing and adherence on cholesterol outcomes in diabetes patients;
- determine the cost-effectiveness of statins for primary prevention of cardiovascular and cerebrovascular events in newly diagnosed type 2 diabetes patients taking adherence into account.

In **Chapter 1** a meta-analysis is presented in which we aimed to determine the effect of standard-dose statin treatment on the risk of cardiovascular and cerebrovascular events in a diabetes population without cardiovascular history. In **Chapter 2** meta-analyses are presented in which the effects of standard-dose and intensive-dose treatment are determined in a secondary prevention population. The effect of dose and adherence to statins on LDL-cholesterol outcomes is determined in a retrospective cohort study in **Chapter 3**.

In **Chapter 4** a cost-effectiveness analysis is presented for primary prevention of cardiovascular and cerebrovascular events in newly diagnosed type 2 diabetes patients. For this analysis the baseline risk of a population with type 2 diabetes is assessed using observational patient data, also the effect of real-world adherence rates on cost-effectiveness is assessed.

Part II. Patient & physician behaviour regarding statin treatment

The aims of the second part are to:

- describe adherence and prescribing patterns of statin treatment in diabetes patients;
- determine patient's preferences for lipid-lowering drugs of diabetes patients.

Chapter 5 describes and evaluates statin prescribing and adherence patterns in relation to LDL-cholesterol response in a diabetes cohort study with two year follow-up after statin initiation. In **Chapter 6** the effect of the occurrence of a cardiovascular event while being on statin treatment on adherence rates is determined in diabetes patients, using a matched cohort design. In the study presented in **Chapter 7** we determined the willingness of patients to continue using lipid-lowering treatment, and the importance they attach to specific treatment characteristics. We explored whether these aspects are influenced by patient characteristics such as age, gender, clinical history and education.

Finally, the main findings of the studies are summarized and discussed in the general discussion.

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PART I

Effects and cost-effectiveness of statin treatment