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## Personalized type 2 diabetes treatment in primary care

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# Introduction

There are almost 500 million people with type 2 diabetes (T2D) worldwide, which makes it one of the most common chronic health conditions in the world (1, 2). Including its complications, it is also the 9<sup>th</sup> leading cause of death in the world, while its prevalence is still increasing (1).

Besides genetics and ageing, risk factors associated with developing T2D are related to lifestyle, such as overweight and obesity, unhealthy diet, smoking and lack of physical activity (1). Type 2 diabetes is characterized by insulin resistance, insulin deficiency, or both. Since insulin is a hormone that regulates blood glucose levels, the consequence is high blood glucose level, also known as hyperglycaemia. The extent of hyperglycaemia is usually assessed by measuring glycosylated haemoglobin A1c (HbA1c) in blood, which reflects glucose control in previous two to three months (3).

Type 2 diabetes is closely related to a condition called metabolic syndrome, which is a combination of having at least three of the following (4):

- being overweight, obese or having excessive waist fat,
- having high triglyceride levels with low high-density lipoprotein cholesterol (HDL-c) levels,
- having high blood pressure level and/or
- having insulin resistance.

Having metabolic syndrome or some of these risk factors increases the risk for cardiovascular complications, which affect more than half of patients with T2D (5). The complications include macrovascular complications, such as myocardial infarction, stroke and heart failure, and microvascular complications, such as renal disease, eye problems, foot ulcers or neuropathies (1, 6). Consequently, patients with T2D suffer from decreased quality of life when compared to the general population and people with other chronic conditions (7). Good management of hyperglycaemia and other risk factors is therefore very important (8, 9).

## **MANAGEMENT OF TYPE 2 DIABETES IN THE NETHERLANDS**

Patients with T2D in the Netherlands are managed in primary care (Figure) but are referred to secondary care if the risk factor levels cannot be sufficiently controlled. General or nurse practitioners regularly measure HbA1c and other risk factor levels, discuss lifestyle changes, the need for visits to other healthcare providers (Figure), and adapt the therapy accordingly (10).

Many management options to lower the cardiovascular risk factors are available. These usually start with lifestyle changes, such as changing the diet, increasing physical activity levels, limiting alcohol and stopping with smoking. Although lifestyle changes can provide meaningful improvements in risk factor levels (11, 12), achiev-

ing and maintaining sufficient changes can be difficult for patients (13-16). If the risk factors cannot be sufficiently controlled with only lifestyle changes, medication should be initiated. For this, many different glucose-, blood pressure- and cholesterol-lowering medicines are available.

Treatment guidelines can help prescribers decide on the best treatment for their patients based on current evidence. Many international and national treatment guidelines are available and regularly updated when new evidence becomes available. The most commonly used guidelines for the management of diseases in primary care in the Netherlands are those published by The Dutch college of general practitioners (*Nederlands Huisartsen Genootschap*; NHG). More specifically, two guidelines are used for patients with T2D: NHG standard for Diabetes mellitus type 2 (10) and NGH standard for Cardiovascular risk management (17).

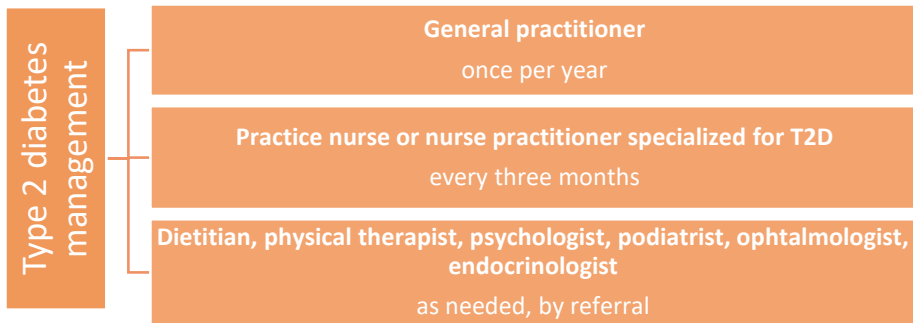


Figure: Management of type 2 diabetes in the Netherlands

## PERSONALIZED TREATMENT OF T2D

Dutch national guidelines started to recommend personalized treatment from 2011 onward. Before 2011, the same target levels for cardiovascular disease risk factors, including HbA1c, systolic blood pressure (SBP) and low-density lipoprotein cholesterol (LDL-c), were recommended for all patients. For example, all patients with T2D should have been treated to reach an HbA1c level below 7% (18). In the last decades, however, concerns have been raised that certain patients, especially older and frail patients with many comorbidities, might not benefit from these strict targets (19-23).

The benefits of preventive cardiovascular risk management are assumed to be seen after several years (24-26), meaning that patients with short life expectancy might not live long enough to benefit from this type of treatment (27). Additionally, the occurrence of adverse drug events, such as hypoglycaemia or hypotension, is often higher in certain subpopulations, including older frail and female patients (23, 28-34). On the other hand, some patients, such as younger patients, those without

cardiovascular complications, with shorter diabetes duration, or long life expectancy, are more likely to benefit from stricter targets in terms of more effectively preventing complications (35). Nevertheless, these stricter targets are recommended only if they can be achieved without increasing the occurrence of adverse events or lead to an unacceptable burden of treatment (35). Given these differences in benefit-risk ratios between patients, treatment recommendations changed over time to provide more personalized care that is suitable for individual patients.

Thus, guidelines nowadays recommend personalized treatment targets, which usually depend on patient characteristics such as age, comorbidities, life expectancy, risk of adverse events, T2D duration, cognitive status, cardiovascular disease risk, current treatment and patients' preferences (8-10, 17). For example, an HbA1c around 8.5% or higher is considered acceptable in older and frail patients, while levels below 7% or even 6.5% are recommended in younger and fit patients. All factors that should influence these personalized targets may not yet be known but more have been added with the guideline updates due to new findings. For instance, the NHG guidelines in 2013 suggested to adapt HbA1c target levels based on age, intensity of diabetes treatment and diabetes duration (36). In addition to these patient characteristics, the guideline from 2021 suggest to take into account also the presence of complications or comorbidities, risk for hypoglycaemia and motivation of the patient when setting these treatment targets (10). Furthermore, guidelines specifically focused on older people have been published (21, 37) which provide more in-depth knowledge and guidance about that population. Nevertheless, certain patient characteristics, such as sex, are currently not included in the guidelines despite findings that females with T2D are at increased risk of cardiovascular and renal disease (38-40) and seem to be more prone to adverse drug events (29, 32, 41).

## **QUALITY OF T2D TREATMENT IN PRIMARY CARE**

Although several treatment options and treatment guidelines are available, many patients do not reach recommended targets and face complications (42-45). Studies using hypothetical cases found that prescribers would initiate medication in all patients at similar HbA1c levels, regardless of patient characteristics (46-48). Furthermore, observational studies illustrated that on one hand patients with T2D may be undertreated (49, 50), while on the other hand too strict levels may be applied for older and frail patients (50-52). The implementation of personalized targets may therefore lag behind. This is of concern and could reflect clinical inertia, defined as the failure to start or stop a therapy or its (de)intensification when appropriate (53-55). Such inertia can occur due to factors related to healthcare professionals, such as lack of

time, patients' preferences, such as not taking the disease serious, and the healthcare system, such as resource constrains (56).

Clinical inertia can lead to potential undertreatment and overtreatment in patients, which can result in poor health outcomes. It is estimated that a substantial part of patients with T2D are potentially undertreated or overtreated when it comes to glycaemic control, where elderly patients and males with T2D are more prone to overtreatment and females are more often undertreated (48, 50, 51, 57-59). Nevertheless, a recent review of studies on sex differences in screening, risk factor control, and drug interventions for T2D found mixed results regarding sex differences in the quality of care (60). Most of the studies evaluated sex differences before 2015 and information about differences in diabetes care from recent years is lacking. Also, many studies looked either at prescribing data or at risk factor control. Studies using prescribing data in relation to risk factor control can provide meaningful insight into current practices and help us gain more understanding of what is needed to improve the quality of treatment (61).

## **PATIENT INVOLVEMENT IN T2D MANAGEMENT**

An important aspect of personalized medicine which gained more attention in the last decades is taking patients' preferences into account. Since T2D is mostly a consequence of lifestyle behaviours, patient involvement is essential in its management (62) and incorporating patient's preferences and needs into treatment decisions can significantly improve treatment outcomes (63, 64). It has been shown that patients differ based on their commitment to lifestyle changes, adherence to medication and the support they need for effective self-management (65). On one hand, different barriers for lifestyle changes have been observed, such as lack of knowledge, money or social support (66, 67). Furthermore, many patients are reluctant to engage in discussions with prescribers regarding changes in their lifestyle or do not wish to participate in lifestyle educational programmes (68). On the other hand, also medication taking can be problematic. One study observed that only 40% of patients with T2D would be willing to take all oral medication needed to reach all treatment targets (69). Knowing patients' preferences for T2D management is therefore essential to create an appropriate treatment plan, but it was observed that such preferences may not be sufficiently evaluated during patient consultations (70). Better insight into patients' preferences and needs for lifestyle changes and medication management can therefore support a more patient-centred decision making process in the future.

## RESEARCH AIMS AND THESIS OUTLINE

With this thesis we aimed to look at how personalized management of T2D is applied in primary care. More specifically, we conducted real world studies to assess if and how diabetes treatment changed over time, where it could be improved, and which patient characteristics might need more attention in making personalized treatment decisions. For these studies, reported in chapters 2 to 7, the Groningen Initiative to Analyse Type 2 Diabetes Treatment (GIANTT; [www.giantt.nl](http://www.giantt.nl)) database was used, which contains anonymous primary care electronic medical records data of more than 60 000 patients with T2D from the north part of the Netherlands. The GIANTT database includes laboratory measurements, diagnoses and prescription information, and is therefore a valuable source of information to assess the quality of T2D treatment in primary care. Furthermore, we conducted a survey study among patients with T2D to assess patients' willingness to engage in different treatment options.

In **chapters 2, 3 and 4** we examined whether the initiation of medication treatment in patients with T2D in primary care was according to the guideline recommendations and whether the implementation of personalized treatment targets could be seen in the period from 2007 to 2020. In **chapter 2** we show trends in HbA1c thresholds at initiation of glucose-lowering medication between the years 2008 and 2014, whereas in **chapter 3** we show trends in SBP thresholds at initiation of blood pressure-lowering medication between the years 2007 and 2014. The influence of age and frailty on these trends in HbA1c and SBP thresholds were assessed. In **chapter 4**, we extended the study period to cover the years 2015 to 2020. In addition, in this chapter we present the impact of sex on these trends.

Since previously observed sex differences in cardiovascular risk could be a consequence of sex disparities in prescribing, we assessed sex differences in the rates of prescribing of glucose-, lipid- and blood pressure-lowering medication in **chapter 5**. We used previously developed and validated prescribing quality indicators (PQIs) (49) to assess prevalent prescribing, starting and intensifying of medication treatment and assessing some medication safety aspects. Furthermore, in **chapter 6** we report on sex differences in blood cholesterol and triglyceride levels across the life span in patients with T2D treated and not treated with statins. We show the possible effect of menopausal status as well as of statin treatment on sex differences, which provides more insight into potentially undertreated populations.

To assess the consequences of treatment to strict risk factors levels, we examined the association between the occurrence of hypotension-related adverse events (hrAEs) and low SBP levels in patients treated with blood pressure-lowering medication in **chapter 7**. More specifically, we looked at differences in the occurrence of hrAEs between patients of different age, sex and polypharmacy.



In the final study (**chapter 8**) we wanted to gain more insight into the patients' perspectives on different types of T2D treatment. Therefore, we conducted a survey study to assess patients' willingness and considerations to engage in lifestyle changes and medication treatment, as well as explore patient factors and beliefs associated with this willingness.

Finally, the findings of all studies are summarized, and the implications for practice and future perspectives are discussed in **chapter 9**.

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