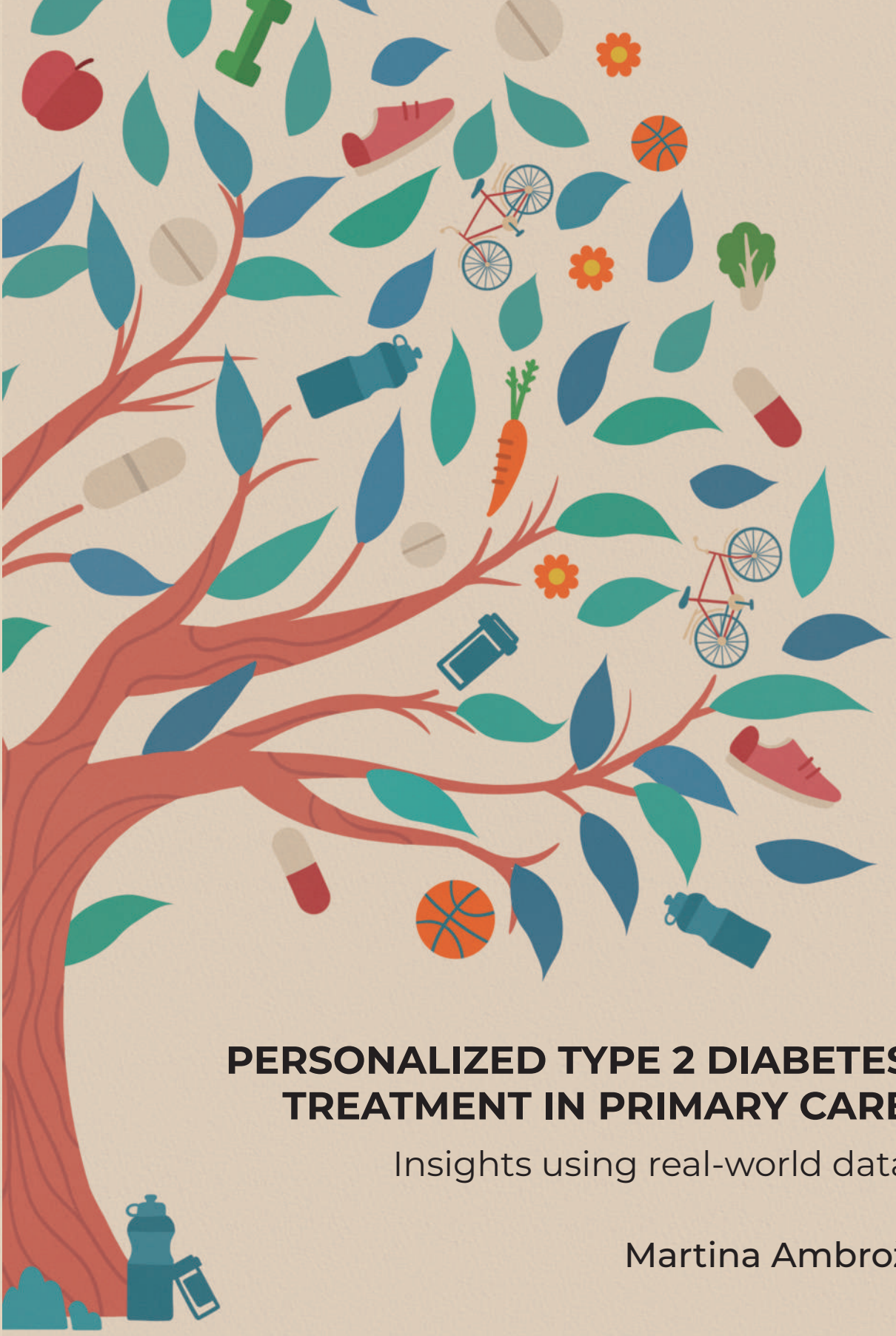

PERSONALIZED TYPE 2 DIABETES TREATMENT IN PRIMARY CARE

Insights using real-world data

Martina Ambrož

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the decision by the College of Deans.

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CONTENTS

1

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 9th 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).

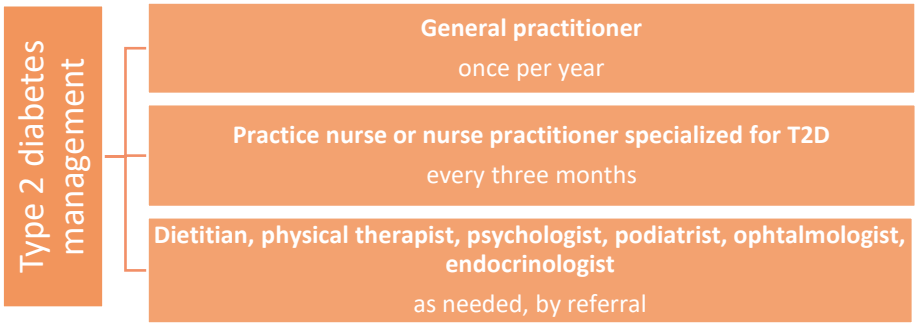

Figure: Management of type 2 diabetes in the Netherlands

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) 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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2

Trends in HbA1c thresholds for initiation of hypoglycaemic agents: impact of changed recommendations for older and frail patients

M Ambrož, ST de Vries, K Hoogenberg, P Denig.

Pharmacoepidemiol Drug Saf. 2021;30:37–44

ABSTRACT

Aims

Less strict glycated haemoglobin (HbA1c) thresholds have been recommended in older and/or frail type 2 diabetes (T2D) patients than in younger and less frail patients for initiating hypoglycaemic agents since 2011. We aimed to assess trends in HbA1c thresholds at initiation of a first hypoglycaemic agent(s) in T2D patients and the influence of age and frailty on these trends.

Materials and Methods

The Groningen Initiative to Analyze Type 2 diabetes Treatment (GIANTT) database was used, which includes primary care T2D patients from the north of the Netherlands. Patients initiating a first non-insulin hypoglycaemic agent(s) between 2008 and 2014 with an HbA1c measurement within 120 days before initiation were included. The influence of calendar year, age or frailty and the interaction between calendar year and age or frailty were assessed using multilevel regression analyses adjusted for confounders.

Results

We included 4 588 patients. The mean HbA1c threshold at treatment initiation was 7.4% up to 2010, decreasing to 7.1% in 2011 and increasing to 7.4% in 2014. This quadratic change over the years was significant ($p<0.001$). Patients aged 60-79 initiated treatment at lower HbA1c and patients of different frailty at similar HbA1c levels. The interaction between year and age or frailty was not significant ($p>0.05$).

Conclusions

HbA1c thresholds at initiation of a first hypoglycaemic agent(s) changed significantly over time, showing a decrease after 2010 and an increase after 2012. The HbA1c threshold at initiation was not influenced by age or frailty, which is in contrast with recommendations for more personalized treatment.

INTRODUCTION

An important goal of type 2 diabetes (T2D) management is reducing the risk of complications by good control of blood glucose levels. This can be achieved with lifestyle changes but hypoglycaemic agents have to be initiated when glucose control is insufficient. The success of T2D management is often monitored by regularly testing glycated haemoglobin (HbA1c) levels, which serve as a measure of chronic hyperglycaemia (1). Several studies showed that the HbA1c level at initiation of a first hypoglycaemic agent is the main predictor of achieving early glycaemic control (2, 3).

Over the last decade, there have been several changes in treatment recommendations for patients with T2D (Supplementary table 1). At first, achieving HbA1c levels below 7% was recommended for most patients (4-6). Between 2008 and 2010, a performance measure assessing the percentage of patients achieving HbA1c levels below 7% was introduced in primary care in the Netherlands (7, 8). Around 2009, several professional organizations started to advocate more personalized HbA1c targets, particularly in elderly patients (9, 10). Diabetes guidelines started to recommend personalized HbA1c treatment targets in 2011. This personalization was based on the patients' age and frailty. From 2011 onwards, guidelines recommended HbA1c targets ≤7.0% for non-frail patients younger than 70 years and between 7.0% and 8.5% for many patients older than 70 years with a longer diabetes duration and/or frail patients (9, 11-13) (Supplementary table 1). These targets are also considered as thresholds for initiating treatment. The extent to which these recommendations have led to more personalized initiation of hypoglycaemic treatment in clinical practice is unknown.

The aim of our study was to investigate trends in HbA1c thresholds at initiation of a first hypoglycaemic agent(s) and the possible impact of more personalized treatment recommendations for older and frail patients with T2D. Given the introduction of performance measures and changes in treatment recommendations, we hypothesized that there would be a decrease in the overall mean HbA1c thresholds in the period 2008-2014 but that first hypoglycaemic agent(s) would be initiated at higher HbA1c thresholds in older and frail patients after more personalized targets were introduced.

MATERIALS AND METHODS

Study design and population

This was a repeated cross-sectional dynamic cohort study for the years 2008 to 2014. We used the data available from the Groningen Initiative to Analyse Type-2 diabetes Treatment (GIANTT; www.giantt.nl) database, which contains anonymous primary care

electronic medical records data from patients with T2D in the northern part of the Netherlands.

For each calendar year, patients were included if they had a confirmed diagnosis of T2D, were 18 years or older, and initiated treatment with a first hypoglycaemic agent(s) in that year. This initiation was defined as a prescription for a non-insulin hypoglycaemic agent (anatomic therapeutic chemical (ATC) classification codes A10B) without a prescription for any hypoglycaemic agent in the preceding 365 days. Included patients had to have at least one year of history in the GIANTT database before initiation of hypoglycaemic treatment. We excluded patients without a documented HbA1c level within 120 days before or on the day of treatment initiation. In addition, patients who had been diagnosed with T2D ten or more years before treatment initiation and patients who initiated treatment with three or more hypoglycaemic agents were excluded since it is unlikely that these patients were true initiators. An approval from the ethics committee is not needed for studies using anonymous medical records data in the Netherlands. We obtained an exemption letter from the University Medical Center Groningen Medical Ethics Review Board (reference number M19.235285).

Outcome variable

The primary outcome was the patient's most recent HbA1c level in the 120 days before or on the day of a first hypoglycaemic agent(s) initiation.

Explanatory variables

The following explanatory variables were included: calendar year of treatment initiation, age or frailty of the patient and the interaction between calendar year and age or frailty. Age was calculated on January 1 of the year in which the patient initiated treatment. We categorized age in four groups (<60 years, 60–69 years, 70–79 years and ≥80 years old) based on the different cut-offs observed among guidelines (Supplementary table 1). Frailty was calculated using an electronic frailty index (eFI), which is based on International Classification of Primary Care (ICPC) coded diagnoses(14). We excluded diabetes from the eFI, thus focussing on differences in additional frailty. A higher number for the eFI indicates a higher degree of frailty. Since there are no validated clinical cut-offs for the eFI, we categorized the scores in tertiles to compare low, medium and high frailty patients.

Confounders

There are several patient characteristics available in the GIANTT database that can be associated with age or frailty and may affect the prescribers' decision to initiate a hypoglycaemic agent. The following were included to correct for potential confounding: sex, duration of diabetes (0-1 year, 2-3 years, 4-5 years, 6-7 years, 8-9 years),

presence of dyslipidaemia (defined as low density lipoproteins (LDL) ≥2.5 mmol/L), systolic blood pressure level (<140 mmHg or ≥140 mmHg), estimated glomerular filtration rate (eGFR; ≤60 mL/min or >60 mL/min), presence of albuminuria (albumin creatinine ratio ≥30 mg/g or albumin in 24h urine ≥300 mg), body mass index (BMI; <24.9 kg/m^2, 25–29.9 kg/m^2 or ≥30 kg/m^2), blood pressure lowering treatment (no treatment, 1 class, 2 classes, ≥3 classes), lipid lowering treatment (no treatment or ≥1 classes) and number of all other prescribed chronic medications at initiation (used as a continuous variable). The most recent laboratory values available in the year before or seven days after initiation were used for these variables. BMI was calculated from weight and height based on the data in the last five years or in the year after initiation or extracted as provided BMI from the database when weight and/or height were not available. The eGFR was calculated from serum creatinine using the Modification of Diet in Renal Disease-4 equation for the years 2008 and 2009, and using the Chronic Kidney Disease Epidemiology Collaboration equation from 2010 onwards, since the standard way of calculating eGFR in the Netherlands changed during the study period (14). In case serum creatinine was not available, the eGFR measurement was extracted as provided in the database. Prescribed chronic medication was assessed in the 120 days before or on the day of treatment initiation.

Missing data

No data for the explanatory variables were missing. When confounders had less than 20% of missing values, they were imputed using multiple imputation by chained equation (MICE) (15). For albuminuria, more than 20% of patients had a missing value. These patients were assumed as not having albuminuria, since conducting this test in the study period was less common in patients without suspected kidney problems.

Analyses

Characteristics of included patients were analysed descriptively per year. We conducted multilevel regression analyses with a two-level random intercept model to account for patients being nested within general practices. First, using the empty model that includes only the outcome variable, we calculated the intraclass correlation coefficient (ICC). The ICC assesses the proportion of variance attributed to general practices. Second, we created the trend model by adding the calendar year and the confounders to the model to assess the overall trend over the years. We compared linear and non-linear trend models using the Wald test to choose the best fitting final model. Next, we assessed the effect of age or frailty on these trends by adding the explanatory variables and the interaction between calendar year and age or frailty on HbA1c levels at initiation in this trend model. To assess changes over time in separate age and frailty groups, additional multilevel analyses were conducted per subgroup.

In these models, the Bonferroni method was used to correct for multiple testing, with a significance level of p<0.0125 when testing for trends per age group and of p<0.0167 when testing for trends per frailty group.

A sensitivity analysis was conducted in which the eFI was used as a continuous variable in the final model.

The analyses were conducted in Stata version 14 (Stata Corp., College Station, TX).

RESULTS

We included 4 588 patients who initiated a first hypoglycaemic agent(s) between 2008 and 2014 (Table 1). The number of patients in each calendar year differed, whereas the patient characteristics were similar over the years (Supplementary table 2). Around 90% of patients initiated treatment with metformin (Figure 1). The use of sulfonylureas slightly decreased over the years from 8% to 6%, mostly on the account of the newer medication that became available in this time period. Complete data were available for 74% of the patients.

Table 1: Characteristics of patients included in the analysis (N=4 588)

Number of patients in source population; N		
	2008 (N = 15 086)	345
	2009 (N = 18 130)	536
	2010 (N = 20 995)	732
	2011 (N = 24 059)	744
	2012 (N = 26 319)	781
	2013 (N = 27 342)	670
	2014 (N = 30 450)	780
Females; N (%)		2 289 (50)
Age in years; N (%)	< 60	1 561 (34)
	60 – 69	1 478 (32)
	70 – 79	1 086 (24)
	≥ 80	463 (10)
Frailty in electronic Frailty Index score; N (%)	0 – 0.03	1 679 (37)
	0.06 – 0.08	1 551 (34)
	0.11 – 0.30	1 358 (30)
Glycated haemoglobin A1c at initiation in %; mean ± SD		7.3 ± 1.1
Fasting glucose; mean ± SD *		8.6 ± 2.2
Diabetes duration; N (%)	0 – 1 years	1 522 (33)
	2 – 3 years	1 384 (30)
	4 – 5 years	881 (19)

Table 1: Characteristics of patients included in the analysis (N=4 588) (continued)

	6 – 7 years	523 (11)
	8 – 9 years	289 (6)
Systolic blood pressure ≥140 mmHg; N (%) [†]		2 263 (54)
BMI in kg/m^2; N (%) [‡]	< 24.9	521 (12)
	25 – 29.9	1 658 (39)
	≥ 30	2 101 (49)
Dyslipidaemia; N (%) [§]		2 631 (65)
eGFR ≤ 60 ml/min/1.73m2; N (%) [¶]		680 (16)
Albuminuria (%) [‖]		52 (1)
Number of chronic medication at initiation; mean ± SD		4.1 ± 2.9
Blood pressure lowering treatment at initiation; N (%)	No treatment	1 477 (32)
	1 class	1 124 (25)
	2 classes	1 077 (23)
	3 or more classes	910 (20)
Treated with a lipid lowering drug; N (%)		2 679 (58)

*Fasting glucose: 1 170 (25.5%) missing values; [†]Systolic blood pressure: 399 (8.7%) missing values; [‡]body mass index (BMI): 308 (6.7 %) missing values; [§]LDL cholesterol: 568 (12.4 %) missing values; [¶]estimated glomerular filtration rate (eGFR): 430(9.4 %) missing values; [‖]albuminuria: 2 353 (51.3%) missing values

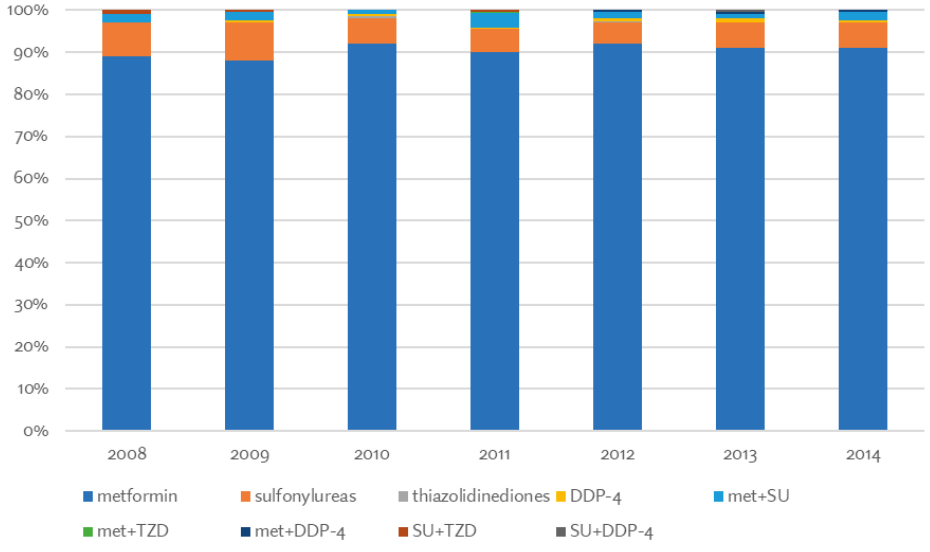

Figure 1: Type of first hypoglycemic agent(s) initiated from 2008 to 2014. DDP-4, dipeptidyl peptidase-4 inhibitor; met, metformin; SU, sulfonylurea; TZD, thiazolidinedione

Trends in HbA1c thresholds

The mean HbA1c level before or at initiation of a first hypoglycaemic agent(s) changed quadratically over the years (β(year)=-0.236, 95% CI -0.334, -0.138, p<0.001; β(year^2)=0.021, 95% CI 0.012, 0.030, p<0.001; joint p using Wald test <0.001; Figure 2A). A stable HbA1c level at treatment initiation of around 7.4% was observed between 2008 and 2010. This was followed by a decrease to 7.1% in 2011 and a rise thereafter to 7.4% in 2014 (Figure 2A, Supplementary table 2).

Of the total variation in HbA1c level at treatment initiation, 6.4% was explained by differences between general practices (ICC = 0.064).

Table 2: Influence of calendar year and age or frailty on glycated haemoglobin A1c (HbA1c) thresholds (multilevel analysis)

	β	95% CI	p	
AGE[†]				
Calendar year	-0.241	-0.338, -0.143	<0.001	<0.001[$]
(Calendar year)^2	0.021	0.012, 0.031	<0.001	
Age <60 years	-0.063	-0.187, 0.061	0.320	
Age 60 – 69 years	-0.256	-0.374, -0.138	0.000	
Age 70 – 79 years	-0.185	-0.301, -0.069	0.002	
Age ≥80 years	reference group			
Interaction year*age	none are significant			
FRAILTY[‡]				
Calendar year	-0.223	-0.321, -0.125	<0.001	<0.001[$]
(Calendar year)^2	0.020	0.011, 0.030	<0.001	
Frailty 0 – 0.03	-0.005	-0.090, 0.081	0.917	
Frailty 0.06 – 0.08	0.057	-0.021, 0.134	0.151	
Frailty 0.11 – 0.36	reference group			
Interaction year*frailty	none are significant			

The intraclass correlation coefficient (ICC) calculated from the empty model was 0.064. [†] The age model was adjusted for sex, duration of diabetes, number of chronic medication at initiation, number of antihypertensive drug classes, systolic blood pressure, lipid lowering therapy, presence of albuminuria, presence of dyslipidaemia, estimated glomerular filtration rate and BMI. [‡] The frailty model was adjusted for sex, systolic blood pressure, duration of diabetes, number of antihypertensive drug classes and lipid lowering therapy. [$]joint significance of calendar year and calendar year^2 using Wald test

Age and frailty

Patients between 60 and 79 years initiated treatment at significantly lower HbA1c levels than younger or older patients (Table 2). The drop in HbA1c thresholds between 2010 and 2011 was visible in all age groups, as was the rise after 2012 (Figure 2B). Although some differences in trends between the age groups can be observed after

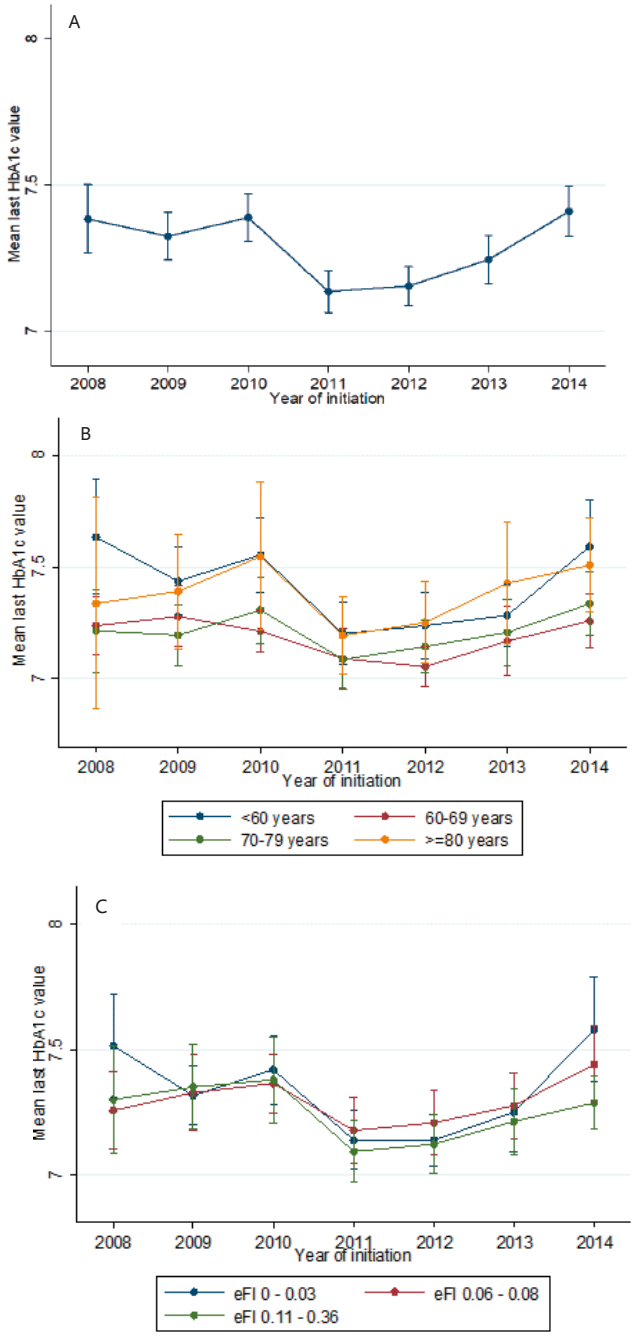

Figure 2: Mean last glycated haemoglobin A1c (HbA1c) levels with 95% confidence intervals before/at initiation of the first hypoglycemic agent(s) from 2008 to 2014 in (A) the whole population, (B) different age groups and (C) different frailty groups. eFI: electronic frailty inde p=0.007; joint p using Wald test =0.008), whereas this trend was not significant in other two groups.

2012, the interaction between age and calendar year was not statistically significant (Table 2). In the analysis per age group, the HbA1c threshold changed significantly over the years in patients younger than 60 years old (β(year)=-0.407, 95% CI -0.608, -0.205, p<0.001; β(year^2)=0.036, 95% CI 0.017, 0.055, p<0.001; joint p using Wald test <0.001) and aged 60 to 69 years (β(year)=-0.216, 95% CI -0.360, -0.072, p=0.003; β(year^2)=0.019, 95% CI 0.005, 0.033,

All frailty groups initiated hypoglycaemic treatment at similar HbA1c thresholds (Figure 2C; Table 2). The interaction between frailty and calendar year was not significant. In the analysis per frailty group, the HbA1c threshold changed significantly over the years in the least frail group (β(year)=-0.345, 95% CI -0.515, -0.176, p<0.001; β(year^2)=0.032, 95% CI 0.016, 0.049, p<0.001; joint p using Wald test <0.001), but this trend was not significant in the other two groups. The sensitivity analysis, using frailty index as a continuous variable, showed similar non-significant results (Supplementary table 3).

DISCUSSION

The mean HbA1c level at initiation of a first hypoglycaemic agent(s) decreased after 2010 and increased after 2012 until the end of our study period in 2014. Surprisingly, there were no differences in the trends for patients of different ages or frailty between 2008 and 2014.

The rising trend in HbA1c level at treatment initiation after 2012 is not in line with our hypothesis since we expected a decrease in the overall HbA1c threshold throughout the study period. It is, however, in line with a recent study conducted in Denmark which assessed the trends in pre-treatment HbA1c levels between 2000 and 2017, where a similar decreasing pattern up to 2011 with a slight increase thereafter was observed (16). Other studies have looked at trends in proportions of patients achieving target levels, showing either increases or non-significant changes over time (17-19). An intriguing finding of our study was that a drop in HbA1c levels was particularly seen between 2010 and 2011. This may be due to policy changes in the Netherlands. In 2008, performance measures were introduced as informative indicators for benchmarking the general practitioners (GPs) on achieving low targets in diabetes patients. In our study region, additional education and support was offered around 2010 to the GPs to improve their performance. We did not expect, however, that the HbA1c would increase after 2012. This could indicate that the performance measures and other activities only had a temporary effect.

Our study showed no differences in HbA1c levels at hypoglycaemic treatment initiation in patients of different ages. This is not in line with our hypothesis and

recommendations of using higher HbA1c targets for older T2D patients after 2011 (Supplementary table 1). Surprisingly, the youngest and the oldest patients initiated treatment at similar slightly higher HbA1c levels. On the one hand, this could be due to more delay in diagnosing diabetes in younger as compared to older patients, who are more actively monitored. This would lead to higher HbA1c levels at diagnosis and subsequently at treatment initiation. It has indeed been shown that the HbA1c levels at diagnosis were higher in younger than in older patients (20, 21). On the other hand, it was found that the time to initiation of a hypoglycaemic agent increased with advancing age (20, 21). Thus, the HbA1c level at treatment initiation can be higher in younger patients because of a delay in diagnosis, while it can be higher in older patients because of a delay in treatment initiation. Interestingly, the HbA1c level at initiation increased after 2012 in all age groups, with this increase being the highest in patients younger than 60 years. We can only speculate about the possible explanations. It could be that either the GPs or the patients prefer to try lifestyle changes for a longer period at a younger age, leading to higher HbA1c levels when deciding to initiate medication. It could also be that GPs became less strict in all patients because potential overtreatment for diabetes has been gaining a lot of attention in the last decade (7).

Similar to age, there were no significant differences between patients with different levels of frailty. Frailty has not been used in previous analyses of hypoglycaemic treatment patterns, however, a recent study observed that patients with three or more comorbidities were more likely to have a tighter glycaemic control than patients with no or only one comorbidity (22). We conducted a post-hoc analysis using the number of chronic medications at initiation as a proxy for frailty and found that patients receiving less than four (median) chronic medications initiated treatment at significantly higher HbA1c levels when compared to four or more chronic medications (Supplementary figure 1 and Supplementary table 4). Furthermore, the observed increase after 2012 particularly in patients prescribed less medication is again unexpected. These results do not support our hypothesis that less strict treatment thresholds were applied for frail patients. A possible explanation could be that frailty measured with the eFI score – or with the number of chronic medication – is not fully applicable or fitting in clinical practice. The eFI was comparable to the Groningen Frailty Index in previous studies (14) but it might not be in line with the GPs' perception of the patient's status. Also, frailty can easily be overlooked in practice due to its subtle manifestations and a lack of consensus on how best to assess it (23). In addition, specific factors such as life expectancy, functional dependency, and risk of hypoglycaemia, which are mentioned in relation to personalized treatment targets, may contribute more to the prescribers' decisions to initiate treatment than frailty in general.

Our study provides important insights in prescribing trends and suggests that trends in initiation of a first hypoglycaemic agent(s) may not be fully in accordance to changes in recommendations towards more personalized treatment. The lack of differentiation between patients of different ages and frailty is of concern. The increase in HbA1c thresholds after 2012 in older patients who do not benefit from tight control is encouraging but this trend was not observed in the most frail patients. Moreover, this trend appeared stronger in the youngest age group, where it is unfavourable and indicates undertreatment of younger and fit patients for whom the disease is not well controlled and can lead to preventable complications. Possible explanations for this observation should be studied further.

Implementing personalized treatment in diabetes may require further support. A study conducted in the period 2010-2012 in seven European countries, in which physicians were first trained to set personalized targets, showed that the targets they set for older patients only marginally deviated from the traditional HbA1c target of 7%. Neither age, duration of diabetes, presence of polypharmacy or frailty had a significant impact on the targets set (24). These results suggest that only issuing new guidelines or providing a training might not be enough to implement personalized diabetes treatment in practice. It has been proposed to offer additional tools or algorithms to support clinical decision-making, which may help in setting more personalized targets in practice (25-27).

The strength of our study is inclusion of a large number of patients using realworld data from primary care. It is also a first study to examine trends in HbA1c level at initiation of a first hypoglycaemic agent(s) and to compare patients of different ages and frailty. Our study has some limitations. Firstly, the number of GPs included in each calendar year fluctuates. Since only little variation was explained at practice level, we do not expect that this affected our conclusions. Secondly, approximately 10% of patients initiating hypoglycaemic therapy were excluded from our analysis because they initiated treatment with insulin. Although it is unlikely that these patients were true initiators, other studies have shown similar rates of initial therapy with insulin in patients with T2D (28, 29). Therefore, we conducted a post-hoc analysis including patients who initiated treatment with insulin, which revealed similar results (data not shown). Thirdly, the observed time between diabetes diagnosis and treatment initiation was quite long for some patients. This could be due to persisting with lifestyle changes for several years before initiating medication treatment. We have to acknowledge, however, that some GPs may have included patients with early stages of diabetes or prediabetes in our cohort. We therefore conducted another post-hoc analysis including only patients with diabetes duration of five years or less (N=3 412), showing similar results (data not shown). Finally, we had some missing data but these were imputed using multiple imputation to reduce possible bias. Frailty, however, was

probably underestimated due to incomplete coding of ICPC diagnoses in electronic medical records.

In conclusion, the observed HbA1c thresholds at initiation of a first hypoglycaemic agent(s) changed significantly over time, showing a decrease after 2010 followed by an increase after 2012. This quadratic trend was not influenced by patients' age or frailty, which is in contrast with changed recommendations for more personalized treatment targets in the study period. More research is needed to determine factors influencing decisions to initiate or refrain from initiating hypoglycaemic treatment in general practice, particularly for frail patients. Furthermore, the reasons for initiating diabetes treatment at increasingly higher HbA1c levels in relatively young patients should be further investigated.

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SUPPLEMENTARY MATERIAL

Supplementary table 1: Overview of changes in Dutch, European and Global type 2 diabetes (T2D) protocol and guideline recommendations regarding glycated haemoglobin A1c (HbA1c) target levels

	Year	HbA1c target	Conditions
NATIONAL			
Diabeteszorg hoogbejaarden[1]	2009	<7.5%	>70 years
		<8%	>80 years
		>8%	if lifetime expectancy <5 years
NHG T2D [2,3]	2006	<7%	all patients
	2013	≤7%	<70 years
		≤7%	>70 years, treated with only lifestyle or metformin
		≤7.5%	>70 years, treated with more than metformin and diabetes duration <10 years
		≤8%	>70 years, treated with more than metformin and diabetes duration >10 years
Verenso [4]	2011	<8.5%	frail elderly (high to very high age, chronically ill, restrictions, multiple morbidity), life expectancy <6 years
EUROPEAN			
ESC/EADS [5]	2007	<6.5%	all patients
EU working party for older T2D patients [6]	2011	7–7.5%	>70 years without major comorbidities
		7.6–8.5%	>70 years and frail (dependent, multisystem disease, care home residents)
GLOBAL			
Global T2D guideline [7,8]	2006	<6.5%	any improvement is beneficial; higher targets are acceptable if there is a high risk of hypoglycemia (insulin, sulfonylureas)
	2012	<7%	higher target is acceptable in presence of hypoglycemia, comorbidities or limited life expectancy
		7–7.5%	>70 years
Managing older T2D patients [9]	2013		>60 years and
		7–7.5%	functionally independent
		7.5–8%	functionally dependent
		<8.5%	functionally dependent and frail

[1] Verhoeven S, Bilo H, van Hateren K, Houweling ST, Kleefstra N, van Meeteren J. Protocol: Diabeteszorg hoogbejaarden in verzorgings- en verpleeghuizen [Protocol: Diabetes care for the very elderly in care and nursing homes]. Diabetes Specialist 2009. [2] Rutten G, De Grauw W, Nijpels G, Goudswaard AN, Uitewaal P, Van der Does F, et al. NHG-Standaard Diabetes mellitus type 2 (tweede herziening) [NHG standard diabetes mellitus type 2 (second review)]. Huisarts en wetenschap 2006;49(3):137-152.

[3] Rutten G, De Grauw W, Nijpels G, Houweling ST, Van de Laar, F A, Bilo HJ, et al. NHG-Standaard Diabetes mellitus type 2 (derde herziening) [NHG standard diabetes mellitus type 2 (third review)]. Huisarts Wet 2013;10(56):512-525. [4] Verenso Richtlijnwerkgroep. Multidisciplinaire Richtlijn Diabetes. Verantwoorde Diabeteszorg bij Kwetsbare Ouderen Thuis en in Verzorgings of Verpleeghuizen. Deel 1. [Multidisciplinary Guideline Diabetes. Responsible Diabetes Care in Vulnerable Elderly at Home and in Residential Care or Nursing Homes. Part 1]. 2011:1-140. [5] Rydén L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer M, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary: The task force on diabetes and cardiovascular diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). European heart journal 2007;28(1):88-136. [6] Sinclair, AJ, Paolisso G, Castro M, Bourdel-Marchasson I, Gadsby R, Rodriguez Mañas L. European diabetes working party for older people 2011 clinical guidelines for type 2 diabetes mellitus. Executive summary. Diabetes & Metabolism 2011;37:S27-S38. [7] IDF Clinical Guidelines Task Force. Global guideline for type 2 diabetes: recommendations for standard, comprehensive, and minimal care. Diabetic Medicine 2006;23(6):579-593. [8] IDF Clinical Guidelines Task Force. Global guideline for type 2 diabetes. Brussels, Belgium: International Diabetes Federation; 2012. [9] IDF Working Group. Managing older People with type 2 diabetes. Brussels, Belgium: International Diabetes Federation; 2013.

Supplementary table 2: Characteristics of included patients over the years

		2008	2009	2010	2011	2012	2013	2014
Number of patients		345	536	732	744	781	670	780
Females; N (%)		165 (48)	257 (48)	394 (54)	360 (48)	401 (51)	319 (48)	393 (50)
Age in years; N (%)	< 60	125 (36)	195 (36)	261 (36)	235 (32)	249 (32)	263 (39)	233 (30)
	60 – 69	118 (34)	187 (35)	229 (31)	233 (31)	268 (34)	193 (29)	250 (32)
	70 - 79	76 (22)	117 (22)	172 (24)	195 (26)	179 (23)	155 (23)	192 (25)
	≥ 80	26 (8)	37 (7)	70 (10)	81 (11)	85 (11)	59 (9)	105 (13)
Frailty in electronic Frailty Index score; N (%)	0 – 0.03	160 (46)	238 (44)	301 (41)	281 (38)	281 (36)	221 (33)	197 (25)
	0.06 – 0.08	112 (32)	186 (35)	242 (33)	247 (33)	263 (34)	241 (36)	260 (33)
	0.11 – 0.36	73 (21)	112 (21)	189 (26)	216 (29)	237 (30)	208 (31)	323 (41)
HbA1c at initiation in %; mean ± SD		7.4 ± 1.1	7.3 ± 1.0	7.4 ± 1.1	7.1 ± 1.0	7.2 ± 0.9	7.2 ± 1.1	7.4 ± 1.2
Fasting glucose; mean ± SD		8.5 ± 2.0	8.5 ± 2.1	8.4 ± 2.2	8.4 ± 2.1	8.4 ± 2.1	8.8 ± 2.4	9.0 ± 2.7
Diabetes duration; N (%)	0 – 1 years	125 (36)	178 (33)	287 (39)	282 (38)	257 (33)	179 (27)	203 (26)
	2 – 3 years	119 (34)	183 (34)	196 (27)	186 (25)	257 (33)	215 (32)	228 (29)
	4 – 5 years	54 (16)	93 (17)	146 (20)	148 (20)	131 (17)	123 (18)	186 (24)
	6 – 7 years	28 (8)	54 (10)	63 (9)	94 (13)	95 (12)	94 (14)	95 (12)
	8 – 9 years	19 (6)	28 (5)	40 (5)	34 (5)	41 (5)	59 (9)	68 (9)
Systolic blood pressure ≥140 mmHg; N (%)		170 (59)	281 (60)	331 (53)	383 (56)	398 (53)	315 (49)	385 (52)
BMI in kg/m^2; N (%)	< 24.9	36 (13)	61 (13)	86 (13)	79 (11)	101 (13)	77 (12)	81 (11)
	25 – 29.9	104 (37)	174 (38)	254 (37)	274 (39)	309 (41)	255 (39)	288 (38)
	> 30	138 (50)	221 (49)	338 (50)	353 (50)	350 (46)	321 (49)	380 (51)
Dyslipidaemia; N (%)		162 (59)	270 (61)	415 (68)	452 (69)	460 (64)	413 (67)	459 (65)
eGFR ≤ 60 mL/min/1.73m^2; N (%)		61 (21)	129 (27)	88 (14)	97 (14)	101 (14)	94 (15)	110 (15)
Albuminuria; N (%)		3 (1)	6 (1)	5 (1)	10 (1)	15 (2)	3 (0)	10 (1)

Supplementary table 2: Characteristics of included patients over the years (continued)

	2008	2009	2010	2011	2012	2013	2014
N of chronic medication at initiation; mean ± SD	3.8 ± 2.7	4.2 ± 3.0	4.1 ± 2.8	4.1 ± 3.0	4.1 ± 3.0	4.0 ± 2.8	4.2 ± 3.1
Blood pressure lowering treatment at initiation; N (%)							
No treatment	115 (33)	166 (31)	229 (31)	228 (31)	255 (33)	225 (34)	259 (33)
1 class	87 (25)	115 (21)	193 (26)	196 (26)	184 (24)	163 (24)	186 (24)
2 classes	78 (23)	150 (28)	148 (20)	182 (24)	181 (23)	154 (23)	184 (24)
3 or more classes	65 (19)	105 (20)	162 (22)	138 (19)	161 (21)	128 (19)	151 (19)
Treated with a lipid lowering drug; N (%)	205 (59)	305 (57)	438 (60)	415 (56)	474 (61)	399 (60)	443 (57)

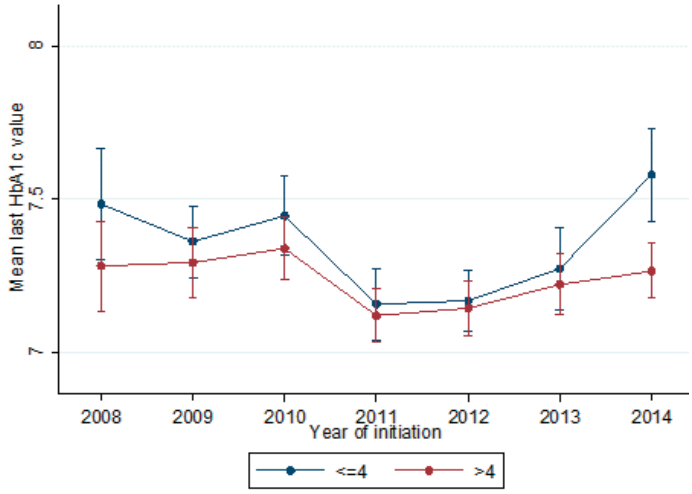
HbA1c: glycated haemoglobin; BMI: body mass index; eGFR: estimated glomerular filtration rate

Supplementary table 3: Influence of calendar year and frailty on glycated haemoglobin A1c (HbA1c) thresholds (multilevel analysis), using frailty index as a continuous variable

	β	95% CI	P	
FRAILTY				
Calendar year	-0.223	-0.321, -0.125	<0.001	<0.001[$]
(Calendar year)^2	0.020	0.011, 0.029	<0.001	
Frailty	0.079	-0.487, 0.644	0.785	
Interaction year*frailty		not significant		

The model was adjusted for sex, duration of diabetes, number of antihypertensive drug classes, lipid lowering therapy and systolic blood pressure

[$]Joint significance of calendar year and calendar year^2 using Wald test



Supplementary figure 1: Mean last glycated haemoglobin A1c (HbA1c) level with 95% confidence intervals (CIs) before or at initiation of a first hypoglycaemic agent(s) through the years in patients with different number of chronic medication at initiation.

Supplementary table 4: Multilevel analysis of number of chronic medication at initiation

	β	95% CI	P	
Calendar year	-0.242	-0.341, -0.144	<0.001	<0.001[$]
(Calendar year)^2	0.022	0.012, 0.031	<0.001	
4 or less chronic medication		reference group		
More than 4 chronic medication	-0.105	-0.167, -0.042	0.001	
Interaction calendar year*N of medication		not significant		

The model was adjusted for sex, duration of diabetes, presence of albuminuria, presence of dyslipidaemia, systolic blood pressure, estimated glomerular filtration rate and body mass index.

[$]Joint significance of calendar year and calendar year^2 using Wald test

3

Changes in blood pressure thresholds for initiating antihypertensive medication in diabetes patients: A repeated cross-sectional study focusing on the impact of age and frailty

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ABSTRACT

Objective

To assess trends in systolic blood pressure (SBP) thresholds at initiation of antihypertensive treatment in patients with type 2 diabetes and the impact of age and frailty on these trends.

Study design and setting

A repeated cross-sectional cohort study (2007–2014) using the Groningen Initiative to Analyse Type 2 diabetes Treatment database was conducted. The influence of calendar year, age or frailty and the interaction between year and age or frailty on SBP thresholds were assessed using multilevel regression analyses adjusted for potential confounders.

Results

We included 4 819 patients. The mean SBP at treatment initiation was 157 mm Hg in 2007, rising to 158 mm Hg in 2009 and decreasing to 151 mm Hg in 2014. This quadratic trend was significant ($p<0.001$). Older patients initiated treatment at higher SBP, but similar decreasing trends after 2009 were observed in all age groups. There were no significant differences in SBP thresholds between patients with different frailty groups. The association between year and SBP threshold was not influenced by age or frailty.

Conclusion

After an initial rise, the observed SBP thresholds decreased over time and were not influenced by age or frailty. This is in contrast with changed guideline recommendations towards more personalised treatment during the study period and illustrates that changing prescribing practice may take considerable time. Patient-specific algorithms and tools focusing on when and when not to initiate treatment could be helpful to support personalised diabetes care.

INTRODUCTION

Treatment of hypertension in patients with type 2 diabetes (T2D) reduces cardiovascular risk, but guideline recommendations on when to initiate antihypertensive treatment to best balance the benefits and risks of treatment have changed over time. In the past, the recommended systolic blood pressure (SBP) threshold for treatment initiation ranged from 130mmHg to 140mmHg (1-7). A personalized approach, however, has been advocated in the last decade for older and/or frail patients, who are at increased risk of adverse outcomes related to low BP levels (4,6,7). Since 2011, treatment guidelines started to recommend higher SBP thresholds in these patients (Figure 1; 3-11). A recent interview study showed that Dutch general practitioners were indeed somewhat reluctant to initiate antihypertensive treatment in older and/or frail patients (12). Studies showing at which SBP thresholds physicians initiate antihypertensive treatment in older or frail patients are lacking.

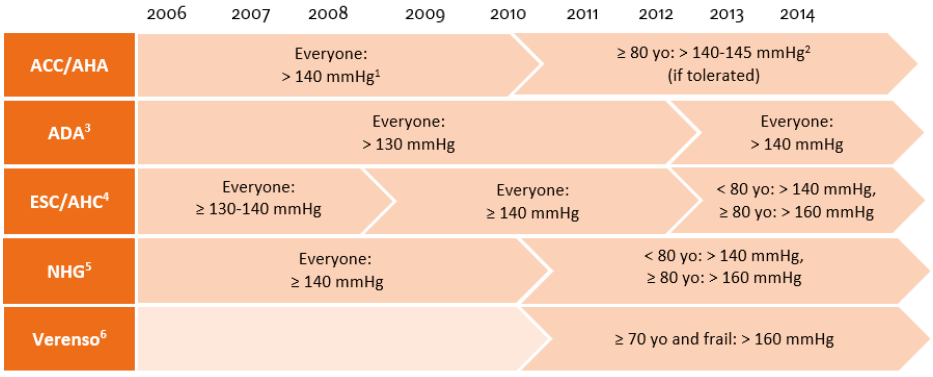

Figure 1: American, European and Dutch guideline recommended systolic blood pressure values for initiation of antihypertensive treatment in patients with type 2 diabetes over the years (1=American College of Cardiology/American Heart Association (ACC/AHA) guidelines (8); 2=ACC/AHA Expert Consensus Document on Hypertension in the Elderly (4); 3=American Diabetes Association (ADA) Standards of Medical Care in Diabetes (3, 9); 4=European Society of Cardiology/Euro Heart Care (ESC/EHC) guidelines for hypertension management (5, 6, 10); 5=Dutch College of General Practitioners (NHG) cardiovascular risk management guidelines (1, 11); 6=Verenso multidisciplinary guidelines for the management of diabetes (7)). yo = years old

A Danish study observed an average SBP level in the general population of 148mmHg before they received antihypertensive treatment in the period from 1976 to 2004 (13). Trend studies on antihypertensive medication use and hypertension control in individuals with T2D show that the percentage of people achieving the recommended SBP target of <140mmHg increased over the last twenty years (14,15). An observational study conducted in the Netherlands showed that the mean achieved SBP decreased from 155mmHg in 1998 to 140mmHg in 2008 in all age groups, with a mean SBP being lower in younger patients. No relevant differences in trends were

observed between different age groups (16). This indicates that blood pressure control in patients with T2D has generally improved over time. The extent to which the more recent personalized guideline recommendations are followed, however, is not clear. This may depend on physician or practice characteristics (17,18), resulting in variability between treatment decisions (19).

The aim of this study was to assess trends in SBP thresholds for initiating antihypertensive medication in patients with T2D and the impact of changed treatment recommendations for older and frail patients. We looked at the period between 2007 and 2014, for which we hypothesized that SBP thresholds would remain similar among young and non-frail patients but would increase among older and/or frail patients. Our secondary aim was to assess to what extent SBP thresholds for treatment initiation varied across general practices.

METHODS

Study design and population

This was a repeated cross-sectional dynamic cohort study for the years 2007 to 2014. The Groningen Initiative to Analyse Type-2 diabetes Treatment (GIANTT; www.giantt.nl) database was used, which contains anonymous electronic medical records data of patients with T2D treated in primary care in the north of the Netherlands.

Patients were included per calendar year when they had a diagnosis of T2D and were ≥18 years. We excluded patients who were not included in the database for at least 365 days before antihypertensive treatment initiation and did not initiate treatment with an antihypertensive (Anatomical Therapeutic Chemical (ATC) codes C03, C04, C07, C08, C09) in that year. Antihypertensive treatment initiation was defined as an initial prescription without a prescription of any antihypertensive drug in the preceding 365 days. Furthermore, patients were excluded when they did not have a documented SBP level within 120 days before or at the day of treatment initiation or when they initiated treatment with three or more drug classes, since it is unlikely that this was a true initiation. It is assumed that these are patients with prevalent antihypertensive treatment, who entered the dynamic cohort during the study period. Moreover, we excluded patients initiating propranolol or a loop diuretic (furosemide, bumetanide), since these are commonly prescribed for other indications (i.e migraine prophylaxis or short-term use in patients with edema, respectively). No approval from an ethics committee is needed for studies using data from anonymous medical records in the Netherlands. An exemption letter from University Medical Center Groningen Medical Ethics Review Board was obtained (reference number M19.235285).

Outcome variable

The outcome was the patient's most recent office SBP level in the 120 days before or on the day of antihypertensive treatment initiation.

Explanatory variables

The following explanatory variables were included: calendar year, age or frailty of the patient and the interaction between year and age or frailty. Age was calculated on January 1 of each year and was categorized in four groups (<60 years, 60–69 years, 70–79 years and ≥80 years) related to cut-off values mentioned in several guidelines (7,11,20). Frailty was calculated using a previously developed electronic frailty index (eFI), which is based on 140 International Classification of Primary Care (ICPC) coded symptoms and diagnoses from the medical history as well as the existence of polypharmacy (21). These ICPC codes are grouped into 36 deficits, for which patients get points. For chronic conditions, a diagnostic code anytime in the past is included, whereas for short-term or episodic conditions only diagnostic codes from the past year are included. The sum of the points from the deficits divided by 36 is the indication of frailty and can take a value between 0 (patient has no deficits) and 1 (patient has all possible deficits). Since all included patients had diabetes, we excluded diabetes from the eFI, thus focusing on additional frailty. There are no validated clinical cut-off values for the eFI, therefore, we categorized the scores in tertiles based on the eFI values in our study population to compare less-, medium- and more frail patients.

Confounders

The following patient characteristics were included as possible confounders: sex, diabetes duration (<2 years or ≥2 years), presence of dyslipidemia (LDL ≥2.5 mmol/L), glycated hemoglobin level (HbA_{1c} <7% or ≥7%), estimated glomerular filtration rate (eGFR; ≤60 mL/min or >60 mL/min), presence of elevated albuminuria (albumin creatinine ratio ≥30 mg/g or albumin in 24h urine ≥300 mg), history of cardiovascular events (presence yes/no of myocardial disease, heart failure or stroke), body mass index (BMI; <24.9 kg/m^2, 25–29.9 kg/m^2 or ≥30 kg/m^2), number of prescribed chronic medication (continuous variable), number and type of glucose lowering treatment (none, one oral, two oral, three or more oral and/or insulin), and lipid lowering treatment (none or one/more drug classes). The most recent laboratory values available in the 365 days before or seven days after treatment initiation were used. BMI was calculated from weight and height or extracted from the database in case these were not available. The eGFR was calculated from serum creatinine using the Modification of Diet in Renal Disease-4 equation for the years 2007 to 2009, and using the Chronic Kidney Disease Epidemiology Collaboration equation from 2010 onwards, since the standard way of calculating eGFR in the Netherlands changed during the study period

(22). In case serum creatinine was not available, the eGFR was extracted from the database when available. Prescribed medication was assessed in the 120 days before or at the day of treatment initiation.

Missing data

There were no missing data for the explanatory variables. Values of confounders with <20% of missing values were imputed using multiple imputation by chained equation (23). For patients without albuminuria measurements (47%), we assumed that they did not have elevated albuminuria, since urine samples were less likely to be collected in our study period for patients without suspected renal function problems.

Analyses

Descriptive statistics were performed to examine patient characteristics per calendar year.

We conducted multilevel regression analyses with a two-level random intercept model to account for patients being nested within general practices. First, using the empty model, which includes only the outcome variable, we calculated the intraclass correlation coefficient to assess the variance that is attributed to general practices. Second, we added the confounders to assess the overall trend over the years. We compared a linear and a quadratic model using the Wald test to choose the best fitting final model. In the final model we assessed the effect of age or frailty on the trends by adding the explanatory variables and the interaction between year and age or frailty on SBP levels at treatment initiation.

Additional subgroup analyses were conducted for each age and frailty group to assess changes over time in these subpopulations using the final model. After applying Bonferroni correction for multiple testing, significance levels were set at $p<0.0125$ (per age group) and $p<0.0167$ (per frailty group).

Furthermore, we conducted sensitivity analyses using the average of the last two SBP levels instead of a single SBP measurement and using eFI as a continuous variable in the final model.

The analyses were conducted in Stata version 14 (Stata Corp., College Station, TX).

Patient and public involvement

Patients and public were not involved in this study.

RESULTS

A total of 4 819 patients initiating antihypertensive treatment in the period 2007 to 2014 were included (Table 1). A flow chart of excluded patients per calendar year is presented in Supplementary Figure 1. Patient characteristics were generally similar throughout the years (Supplementary Table1). Seventy-four percent of included patients had no missing values.

Table 1: Characteristics of included patients (N = 4 819)

Calendar year		**Included patients**
	2007	328
	2008	423
	2009	564
	2010	591
	2011	811
	2012	735
	2013	718
	2014	649
Females; N (%)		2 259 (47)
Age in years; N (%)		
	< 60	1620 (34)
	60 – 69	1 585 (33)
	70 – 79	1 068 (22)
	≥ 80	546 (11)
Frailty in electronic Frailty Index score; N (%)		
	Less frail: 0 – 0.03	2 070 (43)
	Medium frail: 0.06 – 0.09	1 628 (34)
	More frail: 0.11 – 0.40	1 121 (23)
Systolic BP at initiation in mmHg; mean ± SD		155 ± 22
Diastolic BP at initiation in mmHg; mean ± SD		85 ± 12
Diabetes duration <2 years; N (%)		1 259 (26)
HbA_{1c} < 7%; N (%) †		2 717 (61)
BMI in kg/m^2; N (%) ‡		
	< 24.9	751 (17)
	25 – 29.9	1 788 (41)
	≥ 30	1 853 (42)
Dyslipidaemia; N (%) §		2 263 (57)
eGFR ≤ 60 ml/min/1.73m2; N (%) ¶		542 (13)
Elevated albuminuria (%) ‖		101 (4)

Table 1: Characteristics of included patients (N = 4 819) (continued)

History of cardiovascular disease; N (%)	
Myocardial disease[1]	263 (5)
Heart failure[2]	90 (2)
Stroke[3]	212 (4)
Number of chronic medication at initiation; mean ± SD	3.6 ± 2.5
Glucose lowering medication at initiation; N (%)	
No medication	1 269 (26)
1 oral	1 937 (40)
2 oral	982 (21)
3 oral or more and/or insulin	631 (13)
Treated with a lipid lowering drug; N (%)	2 749 (57)
Initiated drug class; N (%)	
Renin-angiotensin-aldosterone system inhibitor	2 645 (55)
Diuretic	762 (16)
Beta blocker	689 (14)
Calcium channel blocker	240 (5)
Combination of antihypertensives	474 (10)

[†]hemoglobin A1C (HbA_{1c}): 352 (7.3 %) missing values; [‡]BMI: 427 (8.9 %) missing values; [§] LDL-cholesterol: 874 (18.1 %) missing values; [¶] estimated glomerular filtration rate (eGFR): 677 (14.0 %) missing values; [||] albuminuria: 2 274 (47.2%) missing values; [1] acute myocardial infarction (ICPC code K75) in the last year or other/chronic ischaemic heart disease (ICPC code K76) anytime in history; [2] heart failure (ICPC code K77) anytime in history; [3] transient cerebral ischemia (ICPC code K89) in the last year or stroke/cerebrovascular incident (ICPC code K90) anytime in history

Trends in SBP thresholds

The mean SBP level at antihypertensive treatment initiation significantly changed over time from 157mmHg (SD 22mmHg) in 2007, rising to 158mmHg (SD 21mmHg) in 2009 and thereafter decreasing to 151mmHg (SD 22mmHg) in 2014 (Figure 2A). This quadratic trend was statistically significant (p<0.001).

Age and frailty

Older patients initiated treatment at significantly higher SBP thresholds than younger patients but age did not significantly influence the relationship between calendar year and SBP threshold (Table 2, Figure 2B). In the analyses per age group, the SBP level at initiation changed significantly (quadratic model) over the years in patients aged between 60 and 69 years (p=0.001).

Frailty did not influence SBP thresholds for treatment initiation and it did not significantly influence the relationship between calendar year and SBP threshold (Table 2, Figure 2C). In the analyses per frailty group, the SBP level at initiation changed significantly (quadratic model) over the years in the less frail (eFI 0-0.03; p<0.001) and more frail (eFI 0.11-0.40; p=0.001) patients.

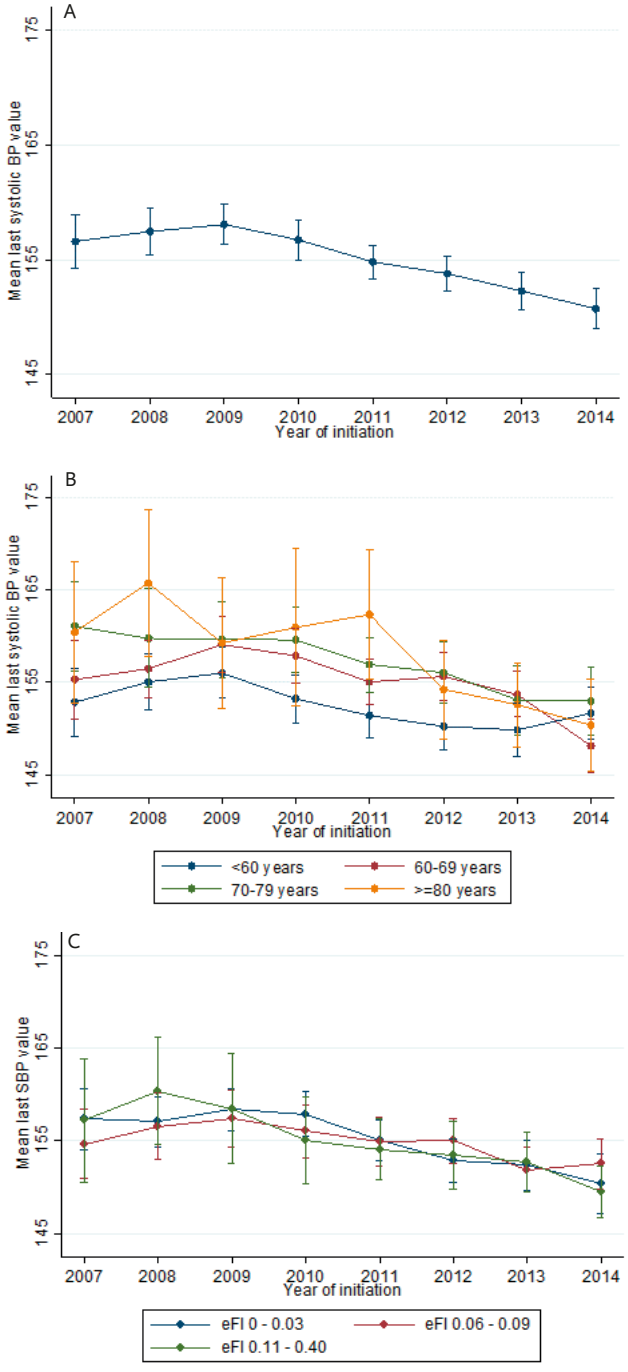

Figure 2: Mean last systolic blood pressure (BP) value with 95% CIs before/at antihypertensive treatment initiation (A) through the years; (B) through the years in different age groups; (C) through the years in different frailty groups. eFI, electronic Frailty Index.

The sensitivity analyses using the mean of the last two SBP levels (Supplementary Figure 2A-C and Supplementary Table 2) and using eFI as a continuous variable (Supplementary Table 3) showed similar results.

Variation between general practices

Of the total variation in SBP level at antihypertensive treatment initiation, 3.2% could be explained by differences between general practices (Table 2, ICC=0.032).

Table 2: Influence of calendar year and age or frailty on blood pressure thresholds (multilevel analysis)

	β	95% CI		P
AGE[†]				
Calendar year	-0.107	-1.429, 1.215	0.874	<0.001[§]
(Calendar year)^2	-0.111	-0.248, 0.027	0.114	
Age <60 years	-8.066	-10.411, -5.723		<0.001
Age 60 – 69 years	-4.115	-6.369, -1.861		<0.001
Age 70 – 79 years	-1.168	-3.407, 1.072		0.307
Age ≥80 years		reference group		
Interaction year*age		none are significant		
FRAILTY[‡]				
Calendar year	0.247	-1.100, 1.593	0.719	<0.001[§]
(Calendar year)^2	-0.159	-0.299, -0.018	0.027	
Frailty 0 – 0.03	-0.060	-1.734, 1.614	0.944	
Frailty 0.06 – 0.09	0.127	-1.519, 1.772	0.880	
Frailty 0.11 – 0.40		reference group		
Interaction year*frailty		none are significant		

The intraclass correlation coefficient (ICC) calculated from the empty model was 0.032. [†] The age model was adjusted for sex, duration of diabetes, number of chronic medication at initiation, number and/or type of glucose lowering therapy, lipid lowering therapy, presence of albuminuria, presence of dyslipidaemia, haemoglobin A1C, history of cardiovascular events, estimated glomerular filtration rate and BMI

[‡] The frailty model was adjusted for sex, duration of diabetes, number and/or type of glucose lowering therapy, lipid lowering therapy and HbA_{1c}. [§] joined significance of calendar year and calendar year^2 using Wald test

DISCUSSION

Summary

This study shows that, after an initial rise up to 2009, SBP thresholds for antihypertensive treatment initiation decreased over time in a large cohort of patients with T2D treated in primary care. This trend occurred regardless of age and frailty, which was in contrast to our hypothesis given the changes in guideline recommendations. The variation in SBP thresholds for treatment initiation that could be attributed to general practices was small.

Strengths and limitations

The strength of our study is the large number of patients included using realworld data. Furthermore, it is a first study investigating trends in SBP thresholds at initiation of antihypertensive treatment. We focussed on the period from 2007 to 2014, expecting that the shift towards more personalized diabetes care around 2011 could be observed during this period. It is possible that changes occurred in more recent years. The first limitation is the fluctuating number of general practices over the years, with different numbers of patients and practices included in each year cohort. Since little variation was explained at practice level, it is unlikely that this affected our primary findings. Second, there were some demographic differences between the patients with and without missing data (Supplementary Table 4). This bias was reduced by multiple imputation (24). Third, we could not include smoking or date of hypertension diagnosis as confounders due to amount and variability of missing values over the years. Furthermore, ICPC codes do not provide information about the severity of the comorbidities. Therefore, there may be some residual confounding which was not accounted for. Fourth, incomplete coding of ICPC diagnoses in electronic medical records may result in underestimation of frailty. Finally, SBP levels show intra-individual variability and may include higher values caused by 'white coat' hypertension (25). However, analysis of the mean last two SBP levels did not change our main findings.

Comparison with existing literature

The observed trends are not in line with changes in treatment guidelines, where higher thresholds were recommended in the older and/or frail patients, particularly in the later years. Several reasons can explain this discrepancy between our hypothesis and findings. First, Dutch healthcare practitioners may have felt pressured to initiate antihypertensive treatment at lower SBP levels in all diabetes patients after the introduction of performance indicators in 2007 (26). From 2008 onwards, they received yearly feedback on the percentage of patients achieving SBP levels of <140mmHg in their own practice as compared to other practices in the region. Although a previous study in this population did not show an increase in overtreatment after the introduction of performance indicators (27), concerns about the negative impact of such measures have been raised (28). In addition, nurse practitioners increasingly became the pivot of diabetes care (26) and their educational material recommended a unified SBP target of 140mmHg at least until the end of our study period (29). It is also possible that the practitioners did not adhere to treatment guidelines either due to lack of familiarity, understanding or agreement with them (30-32). An interview study conducted in 2015 and 2016, however, suggests that Dutch general practitioners did support the idea of using a higher threshold for initiation of antihypertensive treat-

ment in older and frail patients (12). Nevertheless, we demonstrated that guideline changes were not yet implemented more than three years after being published.

Antihypertensive treatment was initiated at relatively high SBP levels in patients of all ages but started to decline after 2009, suggesting that it took many years before the United Kingdom Prospective Diabetes Study (UKPDS) recommended threshold of 140mmHg for treatment initiation was implemented in practice (2). Other studies showed that the percentage of patients achieving an SBP <140mmHg increased in the last two decades but that this increase was smaller in older patients (15). A recent U.S. study showed that the trends in SBP levels in patients ≥60 years decreased until 2010 and remained relatively stable in the six years thereafter (33). Although this study was not restricted to patients with T2D, this seems in contrast with our findings where SBP levels after 2009 decreased in all age groups.

To our surprise, frailty did not influence the SBP threshold for treatment initiation. The frailty range in our study was rather low, which could indicate that antihypertensive treatment is initiated when the patients are still relatively fit. On the other hand, frailty can easily be overlooked due to subtle manifestations, lack of time, or a lack of consensus on the best way to assess it (34). Although the eFI was previously able to identify frailty comparable to the Groningen Frailty Index (21), it might not be in line with the practitioner's perception of a patient's frailty. Therefore, we conducted a post-hoc analysis using the number of chronic medication a patient was receiving at initiation as a proxy for frailty. We observed that the patients being treated with more than three chronic medication (median) initiated treatment at lower SBP levels than those being treated with three or less (Supplementary Figure 3 and Supplementary Table 5). This finding suggests that lower instead of higher thresholds are used for frail patients.

Only a small part of the variation in our study could be attributed to differences between practices. This suggests that patient characteristics determine the threshold to a greater extent than practice characteristics. We only looked at variation between practices which may include decisions of two or more general practitioners within one practice. Unfortunately, we could not conduct analyses at the level of individual practitioners.

Conclusion and implications

The observed SBP thresholds at initiation of antihypertensive treatment decreased after 2009. This trend was not influenced by age or frailty, which is in contrast with changes in treatment recommendations, and may be explained by the introduction of performance indicators. Our study illustrates that changing prescribing practice may take considerable time and only publishing new recommendations might not be sufficient for their successful implementation. On one hand, patient-specific algorithms

and tools to support the timely start of antihypertensive treatment in younger patients are needed. On the other hand, also algorithms and tools to prevent the initiation of too early or strict antihypertensive treatment in older and frail patients should be developed. Furthermore, performance indicators should include the aspect of more personalized treatment recommendations. Further research is needed to assess the underlying reasons and extent of the delay in the implementation of personalized diabetes care and evaluate the impact of strategies to speed up the uptake of recommendations.

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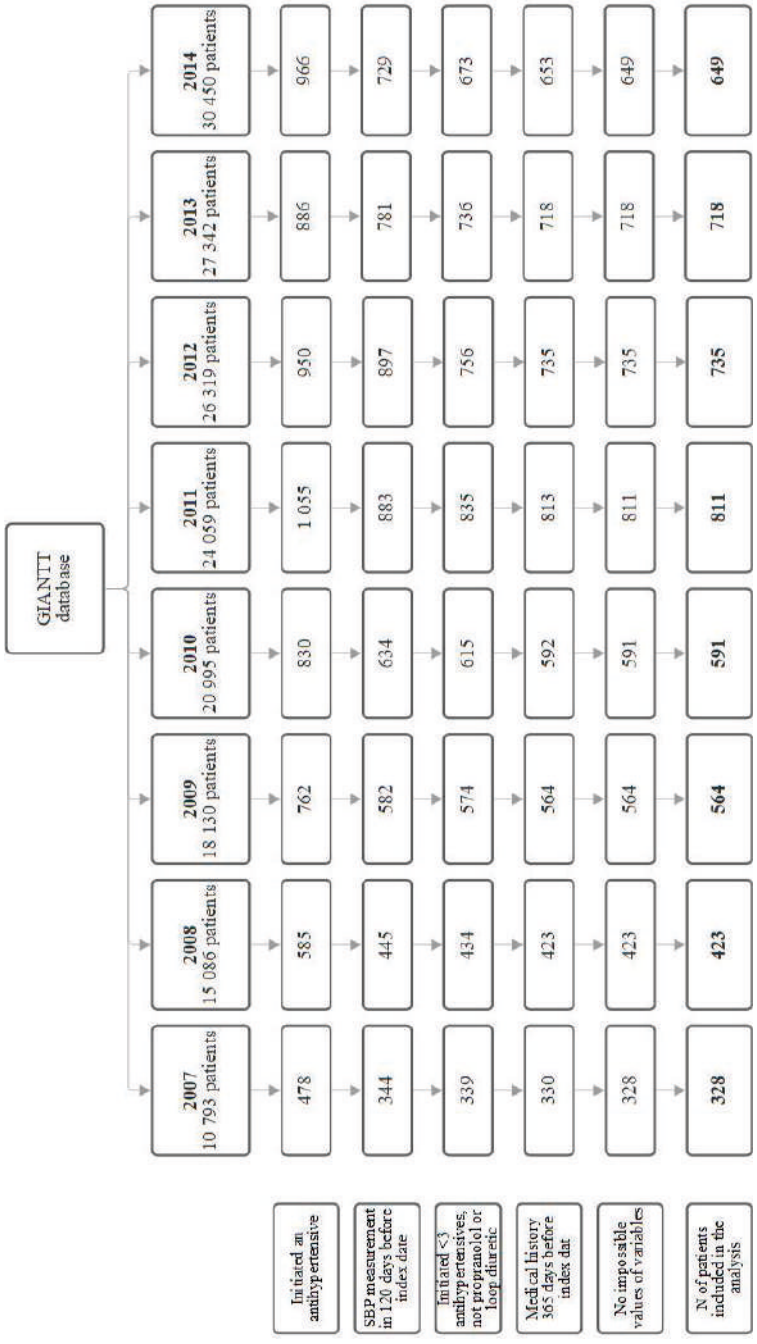
SUPPLEMENTARY MATERIAL

Supplementary material 1



Supplementary Figure 1: Numbers of individuals available at each stage based on the inclusion and exclusion criteria per calendar year

Supplementary Table 1: Characteristics of included patients over the years

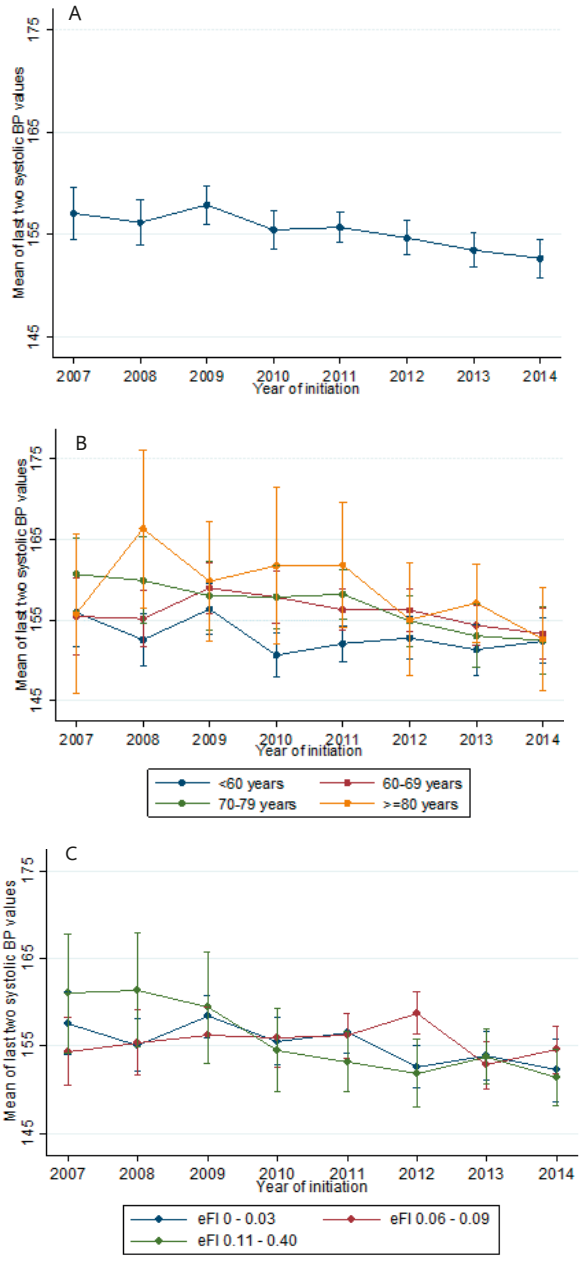
	2007	2008	2009	2010	2011	2012	2013	2014
Number of patients	328	423	564	591	811	735	718	649
Females; N (%)	154 (47)	178 (42)	270 (48)	277 (47)	360 (44)	355 (48)	355 (49)	310 (48)
Age in years; N (%)								
< 60	98 (30)	161 (38)	203 (36)	226 (38)	275 (34)	238 (32)	212 (30)	207 (32)
60 – 69	111 (34)	139 (33)	199 (35)	189 (32)	282 (35)	237 (32)	241 (34)	187 (29)
70 - 79	84 (26)	84 (20)	106 (19)	121 (20)	191 (24)	164 (22)	163 (23)	155 (24)
≥ 80	35 (11)	39 (9)	56 (10)	55 (9)	63 (8)	96 (13)	102 (14)	100 (15)
Frailty in electronic Frailty Index score; N (%)								
Less frail: 0 – 0.03	193 (59)	233 (55)	303 (54)	275 (47)	372 (46)	306 (42)	231 (32)	157 (24)
Medium frail: 0.06 – 0.09	92 (28)	124 (29)	180 (32)	204 (35)	270 (33)	267 (36)	273 (38)	218 (34)
More frail: 0.11 – 0.40	43 (13)	66 (16)	81 (14)	112 (19)	169 (21)	162 (22)	214 (30)	274 (42)
Systolic BP at initiation in mmHg; mean ± SD	157 ± 22	157 ± 21	158 ± 21	157 ± 22	155 ± 21	154 ± 21	152 ± 22	151 ± 22
Diastolic BP at initiation in mmHg; mean ± SD	86 ± 12	87 ± 11	87 ± 12	87 ± 11	86 ± 12	85 ± 12	84 ± 12	84 ± 13
Diabetes duration < 2 years; N (%)	96 (29)	137 (32)	139 (25)	168 (28)	236 (29)	198 (27)	154 (21)	131 (20)
HbA1c < 7%; N (%)	150 (59)	232 (61)	308 (59)	323 (60)	497 (64)	454 (65)	418 (60)	335 (55)
BMI in kg/m^2; N (%) < 24.9	49 (19)	67 (19)	66 (14)	79 (15)	114 (15)	132 (19)	126 (18)	118 (19)
25 – 29.9	100 (39)	142 (39)	218 (46)	222 (42)	312 (40)	280 (40)	283 (41)	231 (38)
> 30	108 (42)	151 (42)	191 (40)	229 (43)	345 (45)	284 (41)	283 (41)	262 (43)
Dyslipidaemia; N (%)	92 (46)	161 (50)	232 (55)	269 (58)	418 (60)	403 (62)	366 (57)	322 (58)
eGFR≤ 60 ml/min/1.73m2; N (%)	37 (17)	45 (14)	69 (15)	44 (9)	70 (10)	93 (14)	100 (15)	84 (14)
Albuminuria; N (%)	5 (4)	9 (4)	12 (4)	10 (3)	15 (4)	16 (4)	18 (5)	16 (4)
History of cardiovascular disease; N (%)								

Supplementary Table 1: Characteristics of included patients over the years (continued)

	2007	2008	2009	2010	2011	2012	2013	2014
Myocardial disease	11 (3)	21 (5)	16 (3)	21 (4)	31 (4)	50 (7)	55 (8)	58 (9)
Heart failure	5 (2)	4 (1)	6 (1)	6 (1)	20 (2)	12 (2)	15 (2)	22 (3)
Stroke	13 (4)	11 (3)	19 (3)	20 (3)	25 (3)	34 (5)	45 (6)	45 (7)
N of chronic medication at initiation; mean ± SD	3.8 ± 2.3	3.3 ± 2.1	3.4 ± 2.4	3.5 ± 2.2	3.4 ± 2.3	3.7 ± 2.6	3.6 ± 2.5	4.0± 2.8
Glucose lowering medication at initiation; N (%)								
No medication	77 (23)	90 (21)	149 (26)	137 (23)	200 (25)	228 (31)	217 (30)	171 (26)
1 oral	129 (39)	179 (42)	199 (35)	247 (42)	363 (45)	271 (37)	283 (39)	266 (41)
2 oral	71 (22)	103 (24)	144 (26)	139 (24)	161 (20)	143 (19)	121 (17)	100 (15)
3 oral or more and/or insulin	51 (16)	51 (12)	72 (13)	68 (12)	87 (11)	93 (13)	97 (14)	112 (17)
Treated with a lipid lowering drug; N (%)	219 (67)	255 (60)	298 (53)	343 (58)	447 (55)	417 (57)	408 (57)	362 (56)
Initiated drug class; N (%)								
Renin-angiotensin-aldosterone system inhibitor	185 (60)	241 (61)	330 (63)	319 (60)	453 (62)	415 (63)	379 (60)	323 (56)
Diuretic	59 (19)	73 (18)	101 (19)	104 (20)	123 (17)	108 (16)	89 (14)	105 (18)
Beta blocker	51 (17)	59 (15)	75 (14)	80 (15)	117 (16)	93 (14)	116 (18)	107 (19)
Calcium channel blocker	14 (5)	22 (6)	21 (4)	29 (5)	32 (4)	40 (6)	44 (7)	38 (7)
Combination of antihypertensives	19 (6)	28 (7)	37 (7)	59 (10)	86 (11)	79 (11)	90 (13)	76 (12)

SUPPLEMENTARY MATERIAL 2

Sensitivity analysis using mean of last two blood pressure measurements (N =2 947)



Supplementary Figure 2: Mean of last two systolic blood pressure (BP) levels with 95% CIs before/at antihypertensive treatment initiation (A) through the years; (B) through the years in different age groups and (C) through the years in different frailty groups.

Supplementary Table 2: Influence of calendar year and age or frailty on blood pressure thresholds (multilevel analysis) using the mean of last two systolic blood pressure measurements

	β	95% CI	P	
AGE*				
Calendar year	-0.894	-2.307, 0.519	0.215	<0.001‡
(Calendar year)^2	-0.001	-0.146, 0.148	0.993	
Age <60 years	-8.367	-10.910, -5.824	<0.001	
Age 60 – 69 years	-4.271	-6.714, -1.828	0.001	
Age 70 – 79 years	-2.921	-5.349, -0.492	0.018	
Age ≥80 years		reference group		
Interaction year*age		none are significant		
FRAILTY†				
Calendar year	-0.867	-2.290, 0.556	0.232	<0.001‡
(Calendar year)^2	-0.013	-0.161, 0.136	0.866	
Frailty 0 – 0.03	-3.501	-5.390, -1.611	0.000	
Frailty 0.06 – 0.09	-1.455	-3.231, 0.322	0.109	
Frailty 0.11 – 0.40		reference group		
Interaction year*frailty		none are significant		

The intraclass correlation coefficient (ICC) calculated from the empty model was 0.050. * The age model was adjusted for sex, duration of diabetes, number of chronic medication at initiation, number and/or type of glucose lowering therapy, lipid lowering therapy, presence of albuminuria, presence of dyslipidaemia, haemoglobin A1C, history of cardiovascular events, estimated glomerular filtration rate and BMI

† The frailty model was adjusted for sex, duration of diabetes, number and/or type of glucose lowering therapy, lipid lowering therapy and haemoglobin A1C. ‡ joint significance of calendar year and calendar year^2 using Wald test

SUPPLEMENTARY MATERIAL 3

Sensitivity analysis using electronic frailty index as a continuous variable There were no statistically significant differences in blood pressure thresholds between patients with different frailty (Supplementary table 3).

Supplementary Table 3: Influence of calendar year and frailty on blood pressure thresholds (multilevel analysis), using frailty index as a continuous variable

	β	95% CI		P	
FRAILTY[†]					
Calendar year	0.211	-1.135, 1.557	0.759		<0.001[‡]
(Calendar year)^2	-0.147	-0.288, -0.007	0.039		
Frailty	-9.324	-20.747, 2.098		0.110	
Interaction year*frailty		none are significant			

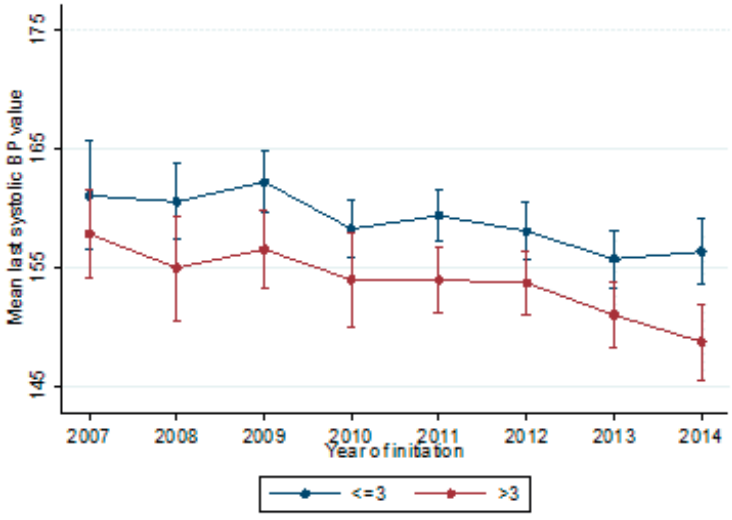
[†] The frailty model was adjusted for sex, duration of diabetes, number and/or type of glucose lowering therapy, lipid lowering therapy and haemoglobin A1C. [‡] joint significance of calendar year and calendar year^2 using Wald test

SUPPLEMENTARY MATERIAL 4

Supplementary Table 4: Characteristics of included patients: comparison of complete cases and cases with missing values

	Complete cases	Cases with missings
Patients; N (%)	3 545 (74)	1 274 (26)
Females; N (%)	1 602 (45)	675 (52)
Age in years; mean ± SD	64 ± 12	65 ± 13
Frailty index; median (Q1 - Q3)	0.08 (0.06 – 0.11)	0.08 (0.03 – 0.11)
SBP at initiation in mmHg; mean ± SD	154 ± 21	158 ± 23
DBP at initiation in mmHg; mean ± SD	85 ± 12	87 ± 13
Diabetes duration in years; mean ± SD	5.4 ± 5.3	5.4 ± 5.5
N of chronic medication at initiation; mean ± SD	3.6 ± 2.4	3.5 ± 2.6
Treated with a lipid lowering drug; N (%)	2 134 (60)	615 (48)
Initiated with one antihypertensive; N (%)	3 215 (91)	1 130 (89)

SUPPLEMENTARY MATERIAL 5



Supplementary Figure 3: Mean last systolic blood pressure value with 95% CIs before/at anti-hypertensive treatment initiation through the years in patients with different number of chronic medication at initiation.

Supplementary Table 5: Multilevel analysis of number of chronic medication at initiation

	β	95% CI		P
Calendar year	-0.206	-1.543, 1.130	0.762	<0.001‡
(Calendar year)^2	-0.101	-0.240, 0.037	0.152	
3 or less chronic medication		reference group		
More than 3 chronic medication	-4.107	-5.428, -2.785		<0.001
Interaction year*N of medication		none are significant		

The model was adjusted for sex, duration of diabetes, number and/or type of glucose lowering therapy, lipid lowering therapy, presence of albuminuria, presence of dyslipidaemia, haemoglobin A1C, estimated glomerular filtration rate and BMI.

‡ Joint significance of calendar year and calendar year^2 using Wald test

4

Less timely initiation of glucose-lowering medication among younger and male patients with diabetes and similar initiation of blood pressure-lowering medication across age and sex: Trends between 2015 and 2020

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ABSTRACT

Aims

We aimed to assess trends in glycosylated hemoglobin A1c (HbA1c) and systolic blood pressure (SBP) thresholds at initiation of glucose- and blood pressure-lowering medication among patients with type 2 diabetes and assess the influence of age and sex on these trends.

Materials and Methods

We used the Groningen Initiative to ANalyze Type 2 diabetes Treatment (GIANTT) primary care database. Patients initiating a first non-insulin glucose-lowering or any blood pressure-lowering medication between 2015 and 2020 with an HbA1c or SBP measurement in the 120 days before initiation were included. We used multilevel regression analyses adjusted for potential confounders to assess the influence of calendar year, age or sex, and the interaction between calendar year and age or sex on trends in HbA1c and SBP thresholds at initiation of medication.

Results

We included 2,671 and 2,128 patients in the analyses of HbA1c and SBP thresholds, respectively. The overall mean HbA1c threshold at initiation of glucose-lowering medication significantly increased from 7.4% in 2015 to 8.0% in 2020 ($p<0.001$), and particularly in the younger age groups. Compared to patients ≥80 years, patients aged 60-69 years initiated medication at lower levels mainly in the first years. Patients <60 years and between 70-79 years initiated medication at similar levels as patients ≥80 years. Females initiated medication at lower levels than males throughout the study period ($p<0.001$). The mean SBP threshold at initiation of blood pressure-lowering medication varied from 145 to 149 mmHg without a clear trend ($p=0.676$). There were no differences in SBP thresholds between patients of different ages or sex.

Conclusions

The rising trend in the HbA1c threshold for initiating glucose-lowering medication in the lower age groups was unexpected and requires further investigation. Males appear to receive less timely initiation of glucose-lowering medication than females. The lack of higher thresholds for the oldest age group or lower thresholds for the youngest age group in recent years is not in line with the age-related recommendations for personalized diabetes care and calls for health systems interventions.

INTRODUCTION

Adequate treatment of risk factors, including glycosylated haemoglobin A1c (HbA1c) and systolic blood pressure (SBP), is important for people with type 2 diabetes mellitus (T2DM) to lower the risk of micro- and macrovascular complications (1, 2). When patients do not achieve recommended HbA1c and SBP target levels with lifestyle changes, medication treatment should be initiated. Timely initiation of medication treatment is important in order to achieve optimal targets and better outcomes (3-5). Optimal targets, however, may differ between patients. In the last decade, treatment guidelines have incorporated more personalized recommendations based on patient factors such as age, frailty, cardiovascular risk, and patient preferences (2, 6-18). Older and more frail patients may require and prefer less aggressive treatment, given the shift in benefit-risk balance of tight risk factor control due to ageing (19-22). Females with T2DM, on the other hand, may need more intensive treatment given their higher relative risks of cardiovascular and renal disease (23-25). Currently, it is unknown to what extent have these changes in treatment recommendations been applied in clinical practice. It is known that dissemination of new recommendations may need additional interventions targeting clinicians to be effective at changing practice patterns (26).

To facilitate the effective and safe use of medication treatment, it is relevant to study drug utilization trends in the whole population as well as among specific subpopulations. A study looking at trends among Dutch T2DM patients showed that mean HbA1c and blood pressure levels decreased between 1998 and 2008 and were similar for different age categories (27). Another study showed a slight decrease in the proportion of patients treated with glucose-lowering medication between 1998 and 2013, with no significant sex differences in treatment or achieving targets in the later years (28). These studies also showed that treatment with blood pressure-lowering medication increased particularly in the early years, with only small differences between the sexes or age groups. Focusing on the initiation of medication, we previously observed little change in the mean HbA1c threshold at initiation of glucose-lowering medication between the years 2008-2014. Despite the changed recommendations towards more personalized treatment, we did not observe higher thresholds among older or frail patients over the years (29). Furthermore, we observed that SBP thresholds at initiation of blood pressure-lowering treatment among T2DM patients decreased in the period 2009-2014, regardless of age or frailty (30).

Little is known about these treatment trends in the recent years. Our aim was to 1) assess trends in HbA1c and SBP thresholds at initiation of glucose- and of blood pressure-lowering treatment between the years 2015 and 2020, and 2) assess the influence of patients' age and sex on these trends.

METHODS

Study design and population

We conducted a repeated cross-sectional dynamic cohort study of the years 2015 to 2020. We used the Groningen Initiative to ANalyze Type 2 diabetes Treatment (GIANTT; www.giantt.nl) database, which contains anonymous electronic medical records data from T2DM patients treated in primary care in the north part of the Netherlands. In the Netherlands, the majority of T2DM patients are managed in primary care, often receiving 3-monthly check-ups by a nurse practitioner and yearly check-ups by their general practitioner. The methods used in this study were similar to those used in previous trend studies using the same database (29, 30).

Patients were included in the calendar year if they initiated treatment with a glucose- or blood pressure-lowering medication, had an HbA1c or SBP measurement, respectively, within 120 days before medication initiation and had at least one year of medical history in the GIANTT database. Medication initiation was defined as a prescription for a non-insulin glucose-lowering medication (anatomic therapeutic chemical [ATC] classification codes A10B) or any blood pressure-lowering medication (ATC codes C03, C04, C07, C08, C09) without a known prescription for any glucose- or blood pressure-lowering medication, respectively, in the preceding 365 days. We excluded patients who were diagnosed with diabetes before the age of 35 years because of the possibility that these were type 1 diabetes patients (31). Patients who initiated treatment with three or more different glucose- or blood pressure-lowering medications, propranolol, or a loop diuretic were also excluded, since these treatments were more likely intensifying pre-existing treatment or were prescribed for other indications (30). Finally, all patients who had T2DM for more than 10 years were excluded from the analysis of HbA1c thresholds since it is unlikely that those were true initiators. We obtained an exemption letter from the University Medical Center Groningen Medical Ethics Review Board (reference number M19.235285) since in the Netherlands no approval is needed for studies using anonymous medical records.

Outcomes and explanatory variables

Our two outcomes were the patients' most recent HbA1c or SBP level in the 120 days before or on the day of glucose- or blood pressure-lowering medication initiation, respectively.

We included the following explanatory variables: calendar year of medication initiation, patients' age or sex and the interaction between calendar year and age or sex. Age was calculated on January 1 of the calendar year in which the patient initiated treatment and was categorized in four groups (<60 years, 60-69 years, 70-79

years, and ≥80 years old) based on the different cut-offs observed among guidelines (2, 6-18). Sex was used as entered in the database.

Confounders

Variables that could be associated with age or sex of the patient, that might affect the decision to initiate glucose- or blood pressure-lowering medication, and that were available in the GIANTT database were included as potential confounders. In particular, female sex and longer diabetes duration are known to be associated with higher age and possibly associated with less aggressive treatment. Also, a higher number of chronic medication and poor renal function, which may prevent the initiation of additional medication, are known to be associated with higher age. On the other hand, elevated cardiovascular risk factors, which differs between age and sex groups, can be associated with more aggressive treatment. For more aggressive initiation of antihypertensive treatment, also a history of cardiovascular disease and smoking are likely to be confounders. Therefore, the following variables were included: sex or age in the analysis of the effect of age or sex, respectively, diabetes duration (0-1 year, 2-3 years, 4-5 years, 6-7 years, 8-9 years, or ≥10 years), presence (yes/no) of dyslipidaemia (defined as low density lipoproteins [LDL] ≥2.5 mmol/L), estimated glomerular filtration rate (eGFR; ≤60 ml/min/1.73 m^2 or >60 ml/min/1.73 m^2), presence of albuminuria (albumin creatinine ratio ≥30 mg/g or albumin in 24 hours urine ≥300 mg), body mass index (BMI; <24.9 kg/m^2, 25-29.9 kg/m^2, or ≥30 kg/m^2), lipid-lowering treatment (no treatment or ≥1 classes) and number of all other prescribed chronic medications at initiation (used as a continuous variable). Additionally, the analyses of HbA1c thresholds were adjusted for SBP level (<140 mmHg or ≥140 mmHg) and blood pressure-lowering treatment (no treatment, 1 class, 2 classes, or ≥3 classes) and the analyses of SBP thresholds for HbA1c level (<7% or ≥7%), history of cardiovascular events (presence yes/no of myocardial disease, heart failure, or stroke), number and type of glucose-lowering treatment (none, one oral, two oral, or three or more oral and/or insulin) and smoking. More details about definitions and calculations of these variables have been described previously (29, 30).

Missing data

No data for the explanatory variables were missing. Confounders which had less than 20% of missing values were imputed using multiple imputation by chained equation (MICE). Imputing variables with large amounts of missing data would be expected to end up with larger error terms. For albuminuria, where more than 20% of patients had a missing value, we assumed these patients did not have albuminuria, since conducting this test is less common in patients without suspected kidney problems.

Analyses

The same analyses were used for the HbA1c and SBP thresholds. Patient characteristics were analysed descriptively per calendar year, age, and sex group. We conducted multilevel regression analyses with a two-level random intercept model to account for patients being nested within general practices. First, using the empty model which includes only the outcome, we calculated the intraclass correlation coefficient to assess the variance that is attributed to general practices. Next, we added the potential confounders to assess the overall trend over the years. This model was also used to analyse the trends in each age and sex group separately, where after applying Bonferroni correction for multiple testing the significance levels were set at $p<0.0125$ for age and $p<0.025$ for sex. Last, to assess the effect of age and sex over time, we added age or sex and the interaction between year and age or sex to the model. All analyses were conducted in Stata V.14 (Stata Corp., College Station, Texas).

RESULTS

There were 2,671 and 2,128 patients who met our in- and exclusion criteria included in the analyses of HbA1c and SBP thresholds, respectively (Supplementary figure 1 and 2). The number of included general practices ranged from 72 in 2015, 78 in 2016-2018, 76 in 2019 to 59 in 2020. The variance explained by the general practices was 6.9% and 5.5%, respectively.

Trends in HbA1c thresholds

The number of patients initiating glucose-lowering medication per year ranged from 348 to 551 (Supplementary figure 1). Thirty-three percent of the included patients were younger than 60 years, 12% were 80 years old or older, 45% were females and 87% initiated treatment with metformin (Table 1). The patient characteristics over the years and per age and sex groups are shown in Supplementary tables 1, 2 and 3. Complete data were available for 76% of the patients.

The overall mean HbA1c thresholds at initiation of glucose-lowering medication significantly increased over the years from 7.4% in 2015 to 8.0% in 2020 (linear trend, β(year)=0.093, 95% CI 0.062, 0.124; $p<0.001$; Figure 1a). In the analysis per age group (Figure 1b), the mean HbA1c threshold significantly increased over time in patients younger than 60 years (linear trend, β(year)=0.086, 95% CI 0.026, 0.147; $p=0.005$) and those aged 60-69 years (linear trend, β(year)=0.182, 95% CI 0.125, 0.239; $p<0.001$). No statistically significant linear nor quadratic trends were seen in the older age groups. In the analyses by sex (Figure 1c), the mean HbA1c threshold significantly increased over time in both males (linear trend, β(year)=0.087, 95%

CI 0.044, 0.130; p<0.001) and females (linear trend, β(year)=0.101, 95% CI 0.056, 0.146; p<0.001). Patients younger than 60 years initiated glucose-lowering treatment at somewhat higher HbA1c levels than older patients in most years (Figure 1b), but this age effect was not statistically significant (Table 2). On the other hand, patients aged 60-69 years initiated treatment at lower levels in the first years and at similar levels in the later years compared to patients aged 80 years or older (Table 2). Females initiated glucose-lowering treatment at significantly lower HbA1c thresholds than males which was seen in all years (Figure 1c and Table 2).

Table 1: Characteristics of patients included in the glycated hemoglobin A1c (HbA1c) threshold analyses (N=2,671)

Females; N (%)		1,205 (45)
Age in years; N (%)	<60	894 (33)
	60–69	792 (30)
	70–79	669 (25)
	≥80	316 (12)
HbA1c at initiation in %; mean ± SD		7.7 ± 1.5
Fasting glucose; mean ± SD [+]		9.1 ± 3.0
Diabetes duration; N (%)	0–1 year	967 (36)
	2–3 years	480 (18)
	4–5 years	482 (18)
	6–7 years	418 (16)
	8–9 years	324 (12)
Systolic blood pressure ≥140 mmHg; N (%) [¶]		1,055 (39)
Body mass index in kg/m^2; N (%) [§]	<25	345 (13)
	25–29.9	948 (35)
	≥30	1,309 (49)
Dyslipidemia; N (%) [¥]		1,454 (54)
Estimated glomerular filtration rate ≤ 60 ml/min/1.73m^2; N (%) [Φ]		461 (17)
Albuminuria; N (%) [II]		33 (1)
Number of chronic medications at initiation; mean ± SD		4.1 ± 3.1
Blood pressure-lowering medication at initiation; N (%)	No treatment	1,025 (38)
	1 medication class	599 (22)
	2 medication classes	559 (21)
	3 or more medication classes	488 (18)
Treated with a lipid-lowering medication; N (%)		1,373 (51)
Initiated medication; N (%)	Metformin	2,328 (87)
	Sulfonylurea	178 (7)
	α-glucosidase inhibitors	1 (0)
	Dipeptidyl peptidase 4 (DDP-4) inhibitor	5 (0)
	Glucagon-like peptide-1 (GLP-1) agonist	2 (0)
	Sodium-glucose transport protein 2 (SGLT2) inhibitor	1 (0)
	Metformin + another medication	151 (6)
	Sulfonylurea + another medication	5 (0)

Missing values: [+] 366 (14%); [¶] 303 (11%); [§] 69 (3%); [¥] 387 (14%); [Φ] 248 (9%) ; [II] 792 (30%)

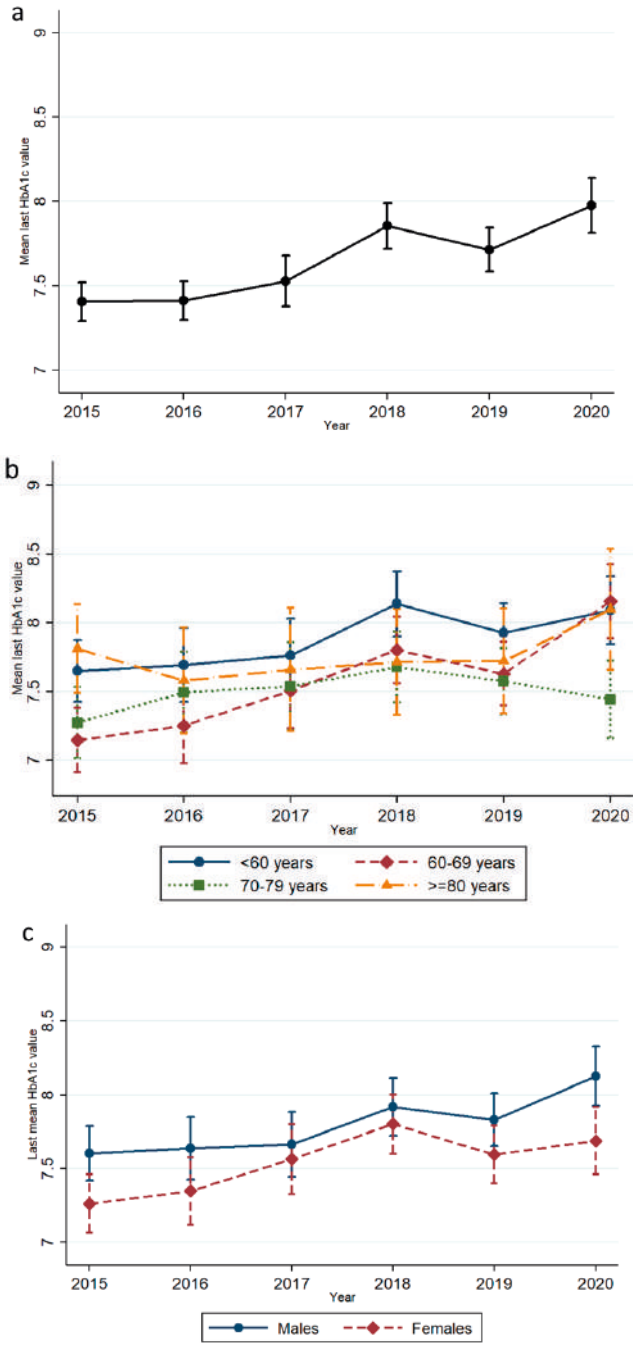

Figure 1: Mean last glycated hemoglobin A1c (HbA1c) levels adjusted for all potential confounders with 95% confidence intervals before/at initiation of the glucose-lowering medication from 2015 to 2020 in (a) the whole population, (b) different age groups, and (c) by sex.

Table 2: Influence of age and sex on glycated hemoglobin A1c thresholds

AGE	β	95% CI	P
Calendar year	0.036	-0.050, 0.122	0.412
Age <60 years	-0.092	-0.481, 0.297	0.642
Age 60 – 69 years	-0.692	-1.081, -0.303	<0.001
Age 70 – 79 years	-0.291	-0.688, 0.107	0.152
Age ≥80 years	Reference group		
Year * Age <60 years	0.056	-0.044, 0.156	0.273
Year * Age 60 – 69 years	0.141	0.039, 0.243	0.007
Year * Age 70 – 79 years	0.006	-0.099, 0.110	0.917
Year * Age ≥80 years	Reference group		
SEX			
Calendar year	0.093	0.062, 0.124	<0.001
Female	-0.252	-0.360, -0.144	<0.001
Male	Reference group		
Interaction female*year	Not significant		

The intraclass correlation coefficient (ICC) calculated from the empty model was 0.069. Multilevel models were adjusted for diabetes duration, number of chronic medications at initiation, number of antihypertensive medication classes, systolic blood pressure, lipid-lowering medication, presence of albuminuria, presence of dyslipidemia, estimated glomerular filtration rate and body mass index, and sex or age in the age and sex analyses, respectively.

Trends in SBP thresholds

The number of patients initiating blood pressure-lowering medication included in our analysis ranged from 272 to 419 (Supplementary figure 2). Twenty-six percent of these patients were younger than 60 years, 17% were 80 years or older and 48% were females (Table 3). Patient characteristics over the years and by age and sex groups are shown in Supplementary tables 4, 5 and 6. Complete data were available for 72% of the patients.

The mean SBP level at initiation of blood pressure-lowering medication rose from 145 mmHg in 2015 to 148 mmHg in 2017, dropped to 145 mmHg in 2019 and went up to 149 mmHg in 2020 (Figure 4a). This was not a significant linear or quadratic trend. There were also no statistically significant trends in the separate age and sex groups.

No significant differences in SBP levels at initiation of blood pressure-lowering medication based on age (Figure 4b) and sex (Figure 4c) were observed (Table 4). The interactions between age or sex and year were also not statistically significant (Table 4).

Table 3: Characteristics of included patients in the systolic blood pressure (BP) analyses (N = 2,128)

Females; N (%)		1,011 (48)
Age in years; N (%)	<60	559 (26)
	60–69	650 (31)
	70–79	566 (27)
	≥80	353 (17)
Systolic BP at initiation in mmHg; mean ± SD		146 ± 21
Diastolic BP at initiation in mmHg; mean ± SD [+]		82 ± 13
Diabetes duration; N (%)	0–1 year	273 (13)
	2–3 years	316 (15)
	4–5 years	276 (13)
	6–7 years	307 (14)
	8–9 years	250 (12)
	≥10 years	706 (33)
Glycated hemoglobin A1c < 7%; N (%) [¶]		1,072 (50)
Body mass index in kg/m^2; N (%) [§]	<25	392 (18)
	25–29.9	823 (39)
	≥30	866 (41)
Dyslipidemia; N (%) [¥]		954 (45)
Estimated glomerular filtration rate ≤ 60 ml/min/1.73m^2; N (%) [Φ]		368 (17)
Albuminuria; N (%) [ll]		68 (3)
Smoking; N (%) [ł]		371 (17)
History of cardiovascular disease; N (%)	Myocardial disease[1]	213 (10)
	Heart failure[2]	84 (4)
	Stroke[3]	114 (5)
Number of chronic medications at initiation; mean ± SD		3.8 ± 2.8
Glucose-lowering medication at initiation; N (%)	No medication	760 (36)
	1 oral	736 (35)
	2 orals	318 (15)
	3 orals or more and/or insulin	314 (15)
Treated with lipid-lowering medication; N (%)		1,073 (50)
Initiated medication; N (%)	Renin-angiotensin-aldosterone system inhibitor	870 (41)
	Combination of antihypertensives	445 (21)
	Beta blocker	345 (16)
	Diuretic	260 (12)
	Calcium channel blocker	208 (10)

Missing values: [+] 3 (0%); [¶] 133 (6%); [§] 47 (2%); [¥] 379 (18%); [Φ] 237 (11%) ; [ll] 552 (26%); [ł] 330 (16%). [1] Acute myocardial infarction (International Classification of Primary Care [ICPC] code K75) in the last year or other/chronic ischemic heart disease (ICPC code K76) anytime in history. [2] Heart failure (ICPC code K77) anytime in history. [3] Transient cerebral ischemia (ICPC code K89) in the last year or stroke/cerebrovascular incident (ICPC code K90) anytime in history.

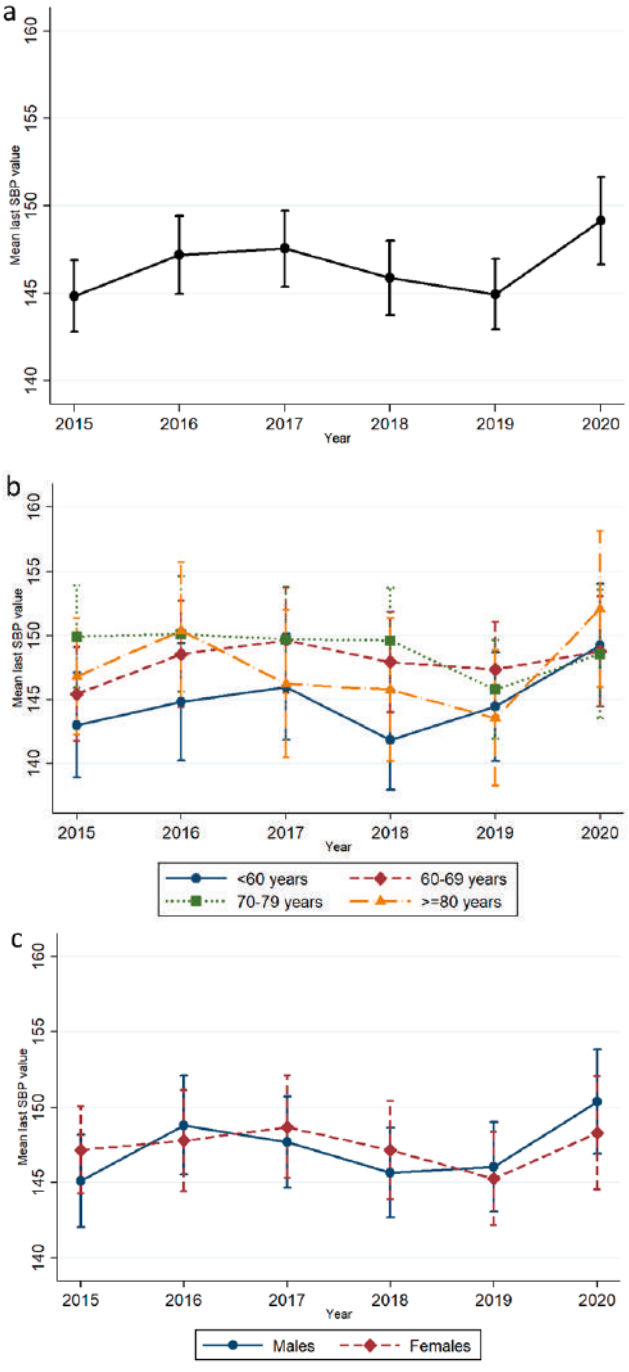

Figure 2: Mean last systolic blood pressure (SBP) levels adjusted for all potential confounders with 95% confidence intervals before/at initiation of the blood pressure-lowering medication from 2015 to 2020 in (a) the whole population, (b) different age groups, and (c) by sex.

Table 4: Influence of age and sex on systolic blood pressure thresholds

AGE	β	95% CI	P
Calendar year	0.104	-0.426, -0.634	0.723
Age <60 years	-2.608	-5.909, 0.693	0.122
Age 60 – 69 years	0.523	-2.468, 3.513	0.732
Age 70 – 79 years	1.499	-1.248, 4.404	0.274
Age ≥80 years		Reference group	
Interactions with year		None are significant	
SEX			
Calendar year	0.113	-0.418, 0.644	0.676
Female	0.170	-1.589, 1.929	0.850
Male		Reference group	
Interaction female*year		Not significant	

The intraclass correlation coefficient (ICC) calculated from the empty model was 0.055. Multilevel models were adjusted for diabetes duration, smoking status, number of chronic medications at initiation, number and/or type of glucose-lowering medication, lipid-lowering medication, presence of albuminuria, presence of dyslipidemia, hemoglobin A1C, history of cardiovascular events, estimated glomerular filtration rate, body mass index, and sex or age in the age and sex analyses, respectively.

DISCUSSION

This study shows that the HbA1c thresholds at initiation of glucose-lowering medication increased over the years 2015 to 2020. This increase was particularly seen in younger age groups and in both males and females. Females generally initiated medication at lower HbA1c thresholds than males. Patients aged 60-69 years initiated medication at lower levels in the first years and at similar levels in the later years compared to patients aged 80 years or older. Patients under 60 years and between 70-79 years initiated medication at similar levels as patients of 80 years and older. The SBP thresholds at initiation of blood pressure-lowering medication remained relatively stable over the study period regardless of age or sex.

We previously observed a rising trend in HbA1c thresholds for medication initiation between 2011 and 2014 (29). The current study adds to this knowledge that this upward trend continued up to the year 2020. Furthermore, the decreasing trend observed in SBP thresholds between 2009 and 2014 (29) appears to have stabilized after 2014.

Looking at studies conducted in other countries, a mixed picture emerges. One study conducted in Denmark showed a decrease in mean pre-treatment HbA1c level between 2000 (9.2%) and 2011 (7.3%) followed by an increase to 7.9% in 2017 (32). These results suggest that prescribers in both Denmark and the Netherlands became less strict regarding the initiation of glucose-lowering medication in recent years. In contrast, a study in the United Kingdom (UK) observed no changes in HbA1c level

at initiation of medication from 2010 to 2017 (33). The HbA1c threshold in 2017, however, was 8.6% in this UK study, which is much higher than the levels observed in Denmark or the Netherlands. Differences in diabetes care between countries have been observed before and could be linked to organizational differences of healthcare systems (34, 35).

Most guidelines recommend initiating glucose-lowering medication at HbA1c levels above 6.5% or 7% in younger patients and above 8% or 8.5% in older patients (6-8, 12, 14, 15). Surprisingly, we did not observe significant differentiation regarding the HbA1c levels at initiation of medication based on age. In particular, we observed similar HbA1c thresholds in patients under 60 years and those aged 80 years or older. These findings indicate potential undertreatment of hyperglycaemia in younger patients, who initiated at mean HbA1c thresholds higher than 7.5% or even 8% in 2020. The recommended SBP threshold for initiation of blood pressure-lowering medication is 130 mmHg or 140 mmHg in younger patients and 150 mmHg or 160 mmHg in older patients (10-12, 17, 18). We observed mean SBP thresholds in all age groups ranging between 140 mmHg and 150 mmHg. These results indicate potential undertreatment of younger patients and potential overtreatment of older patients. Undertreatment of diabetes in younger or male patients has also been shown in Norway and Spain (36, 37) and could be caused by barriers at clinician, patient, and/or healthcare system level (3, 38). Undertreatment of both hyperglycaemia and hypertension in this population is of concern since this can lead to more complications (39-41). Although therapeutic inertia in T2DM has been a well-known problem for many years, it seems that this lack of timely initiation did not change much over the last decade (42). More emphasis and involvement of other healthcare professional, such as pharmacists, might help reduce clinical inertia (43, 44). On the other hand, overtreatment among older T2DM patients has received a lot of attention in the past decade (45) and our study suggests that potential overtreatment at initiation of glucose-lowering medication has decreased over time. That was, however, not the case at initiation of blood pressure-lowering medication, which is of concern, since older patients are more vulnerable for hypotension-related adverse events (19).

Throughout the study period, we observed higher HbA1c thresholds at initiation of glucose-lowering medication in males compared to females. A post-hoc analysis of sex differences in the years 2008-2014 showed the same differences (Supplementary figure 3a). Differences in screening rates are an unlikely explanation, since a recent systematic review observed no clear sex differences in the assessment of cardiovascular risk factors, such as SBP and HbA1c levels, in type 2 diabetes patients (46). However, it could partly be due to later diabetes diagnosis among males. A previous study showed higher HbA1c levels in males than females at diagnosis of diabetes (47). Earlier initiation of glucose-lowering medication in females could also be a

consequence of their increased relative risk for cardiovascular and renal disease (23-25). Additionally, no sex differences in SBP thresholds were observed between 2015 and 2020, but between 2007 and 2009 females initiated blood pressure-lowering treatment at higher SBP thresholds than males (Supplementary figure 3b). This could indicate that some previously identified sex- or gender-related issues leading to undertreatment of cardiovascular diseases among females are diminishing (48).

An intriguing finding was that both mean HbA1c and mean SBP thresholds were highest in 2020. For the HbA1c threshold this could be a continuation of the rising trend over the years, but this is not the case for the SBP threshold. There are indications that the COVID-19 pandemic influenced diabetes care in the year 2020 in the Netherlands (49). Other studies have shown decreases in screening rates, consultations and patient use of healthcare services due to fear of COVID-19 infection (50-52), as well as worse glycaemic and blood pressure control after the beginning of COVID-19 pandemic (53). The impact of this could differ per age group, driven by differences in fear, comorbidity, and frailty. More evidence is needed to assess whether our observations in 2020 were due to the COVID-19 pandemic.

A strength of our study is the use of a large database of real world data from electronic medical records, representing a range of Dutch general practices from urban and rural areas. Data undergo data entry error checks before being imported in the GIANTT database, increasing the internal validity. Using medical record data also brings some limitations. First, this is a dynamic cohort and the variation between years could in part be due to a variation between the participating general practices. We conducted additional analyses of trends in HbA1c and SBP thresholds including only the 59 general practices that were present in the whole period up to the year 2020, which showed similar results (data not shown). Secondly, some patients may not be true initiators but people who moved to a general practice participating in GIANTT while already using medication. Although we included only patients with a medical history of one year, this may not prevent the inclusion of some patients that have been treated with glucose-lowering or blood pressure-lowering medication by other healthcare professionals in the past. We used an arbitrary cut-off of 10 years to exclude patients that were unlikely to be initiators. A previous study conducted in the Netherlands showed that around 20% of patients have not yet started medication treatment three years after their diagnosis (54). Since it is not known what the maximum time to initiation is in our study population, we conducted a post-hoc analysis of the HbA1c thresholds including only patients with a maximum duration of diabetes at medication initiation of five years, which showed similar results (data not shown). A post-hoc analysis of SBP thresholds excluding all patients with a history of cardiovascular disease also did not change the results (data not shown). Another limitation of using medical record data is that we had missing data for some potential confounders, but we used multiple

imputation for confounders with less than 20% missing data to reduce possible bias. Additionally, we conducted a post-hoc analysis also imputing the albuminuria values with more than 20% missing data, which did not change the results (data not shown). Finally, the study was conducted in Dutch primary care and the results may be more generalizable to countries with similar diabetes care systems.

To conclude, the rising trend in the HbA1c threshold for initiating glucose-lowering medication in the lower age groups was unexpected and requires further investigation. The lack of lower thresholds for the youngest age group and higher thresholds for the oldest age group at initiation of glucose- and blood pressure-lowering drugs calls for interventions to support age-related personalized diabetes treatment. Multicomponent interventions targeting clinicians are seen as effective type of interventions (26, 55). This could include educational programs, implementation of decision support tools with specific alerts, feedback reports and other health system interventions. Our finding that males received less timely initiation of glucose-lowering medication than females also need attention. Studies are needed to explore the reasons for as well as the implications of this sex difference. The results of our trend study provide valuable insight into the translation of guideline recommendations into clinical practice, shows areas with room for improvement and can help policy makers to tailor future interventions enhancing appropriate treatment for all patients.

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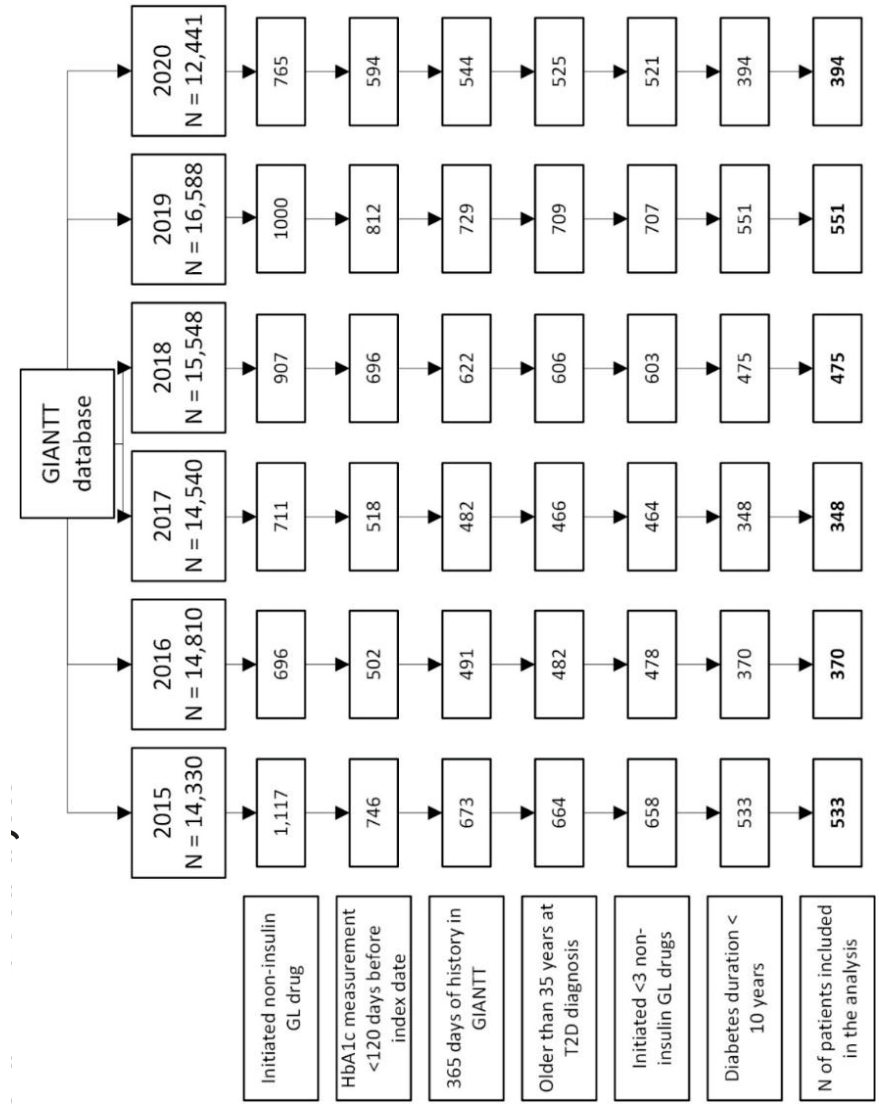
SUPPLEMENTARY MATERIAL 1 – HBA1C ANALYSES



Supplementary figure 1: Number of patients per calendar year in the glycosylated hemoglobin A1c (HbA1c) threshold analyses based on the inclusion and exclusion criteria; GIANTT: Groningen Initiative to ANalyze Type 2 diabetes Treatment; GL: glucose-lowering; T2D: type 2 diabetes

Supplementary table 1: Characteristics of patients included in the glycosylated hemoglobin A1c (HbA1c) analyses over the years

		2015	2016	2017	2018	2019	2020
Number of patients		533	370	348	475	551	394
Females; N (%)		242 (45)	168 (45)	155 (45)	227 (48)	242 (44)	171 (43)
Age in years; N (%)	<60	173 (32)	115 (31)	119 (34)	156 (33)	192 (35)	139 (35)
	60–69	157 (29)	108 (29)	114 (33)	142 (30)	158 (29)	113 (29)
	70–79	124 (23)	93 (25)	77 (22)	125 (26)	148 (27)	102 (26)
	≥80	79 (15)	54 (15)	38 (11)	52 (11)	53 (10)	40 (10)
Glycated hemoglobin A1c at initiation in %; mean ± SD		7.4 ± 1.4	7.4 ± 1.1	7.5 ± 1.4	7.9 ± 1.5	7.7 ± 1.5	8.0 ± 1.6
Fasting glucose; mean ± SD		8.7 ± 2.7	8.8 ± 2.3	9.0 ± 2.7	9.3 ± 3.1	9.4 ± 3.4	9.4 ± 3.2
Diabetes duration; N (%)	0–1 year	241 (45)	77 (21)	73 (21)	192 (40)	217 (39)	167 (42)
	2–3 years	87 (16)	93 (25)	73 (21)	70 (15)	98 (18)	59 (15)
	4–5 years	81 (15)	93 (25)	74 (21)	94 (20)	82 (15)	58 (15)
	6–7 years	58 (11)	63 (17)	78 (22)	82 (17)	78 (14)	59 (15)
	8–9 years	66 (12)	44 (12)	50 (14)	37 (8)	76 (14)	51 (13)
Systolic blood pressure ≥140 mmHg; N (%)		217 (41)	144 (39)	137 (39)	176 (37)	220 (40)	161 (41)
Body mass index in kg/m^2; N (%)	<25	66 (12)	56 (15)	46 (13)	58 (12)	73 (13)	46 (12)
	25–29.9	170 (32)	135 (36)	134 (39)	177 (37)	184 (33)	148 (38)
	≥30	274 (51)	173 (47)	162 (47)	230 (48)	277 (50)	193 (49)
Dyslipidemia; N (%)		284 (53)	195 (53)	189 (54)	254 (53)	313 (57)	219 (56)
Estimated glomerular filtration rate ≤60 mL/min/1.73m^2; N (%)		95 (18)	76 (21)	55 (16)	74 (16)	85 (15)	76 (19)
Albuminuria; N (%)		1 (0)	5 (1)	5 (1)	9 (2)	9 (2)	4 (1)
N of chronic medication at initiation; mean ± SD		4.3 ± 3.2	4.1 ± 3.0	4.3 ± 3.4	4.0 ± 3.1	4.1 ± 3.0	4.0 ± 3.2
Blood pressure-lowering medication at initiation; N (%)	No medication	175 (33)	134 (36)	124 (36)	205 (43)	217 (39)	170 (43)
	1 medication class	121 (23)	79 (21)	90 (26)	101 (21)	126 (23)	82 (21)

Supplementary table 1: Characteristics of patients included in the glycosylated hemoglobin A1c (HbA1c) analyses over the years (continued)

		2015	2016	2017	2018	2019	2020
	2 medication classes	125 (23)	83 (22)	62 (18)	101 (21)	120 (22)	68 (17)
	3 or more medication classes	112 (21)	74 (20)	72 (21)	68 (14)	88 (16)	74 (19)
Treated with a lipid-lowering medication; N (%)		296 (56)	206 (56)	188 (54)	237 (50)	273 (50)	173 (44)
Initiated medication; N (%)	Metformin	441 (83)	321 (87)	288 (83)	422 (89)	497 (90)	359 (91)
	Sulfonylurea	42 (8)	25 (7)	30 (9)	26 (6)	33 (6)	22 (6)
	α-glucosidase inhibitors	1 (0)	-	-	-	-	-
	DDP-4 inhibitor	-	1 (0)	-	2 (0)	1 (0)	1 (0)
	GLP-1 inhibitor	-	-	-	-	-	2 (1)
	SGLT2 inhibitor	-	-	-	-	-	1 (0)
	Metformin + another medication	49 (9)	22 (5)	29 (8)	24 (5)	20 (4)	7 (2)
	Sulfonylurea + another medication	-	1 (0)	1 (0)	1 (0)	-	2 (1)

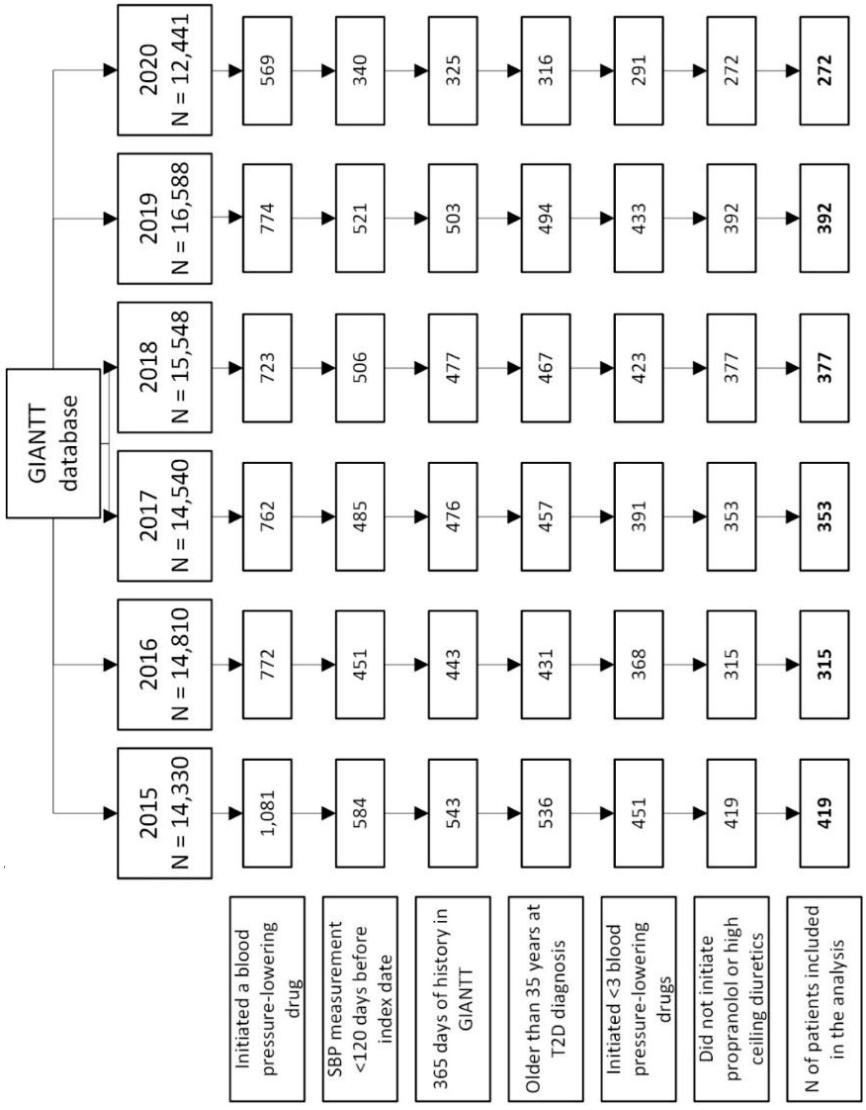
Supplementary table 2: Characteristics of patients included in the glycosylated hemoglobin A1c (HbA1c) analyses per age group

		<60 years	60-69 years	70-79 years	≥80 years
Females; N (%)		391 (44)	324 (41)	310 (46)	180 (57)
Glycated hemoglobin A1c at initiation in %; mean ± SD		7.9 ± 1.6	7.5 ± 1.5	7.4 ± 1.2	7.7 ± 1.3
Fasting glucose; mean ± SD		9.7 ± 3.4	8.9 ± 2.8	8.7 ± 2.3	9.0 ± 3.4
Diabetes duration; N (%)	0 – 1 years	408 (46)	276 (35)	196 (29)	87 (28)
	2 – 3 years	160 (18)	156 (20)	109 (16)	55 (17)
	4 – 5 years	149 (17)	146 (18)	127 (19)	60 (19)
	6 – 7 years	114 (13)	116 (15)	131 (20)	57 (18)
	8 – 9 years	63 (7)	98 (12)	106 (16)	57 (18)
Systolic blood pressure ≥140 mmHg; N (%)		277 (31)	322 (41)	302 (45)	154 (49)
Body mass index in kg/m^2; N (%)	< 24.9	69 (8)	101 (13)	101 (13)	74 (23)
	25 – 29.9	248 (28)	296 (37)	296 (37)	145 (46)
	≥ 30	551 (62)	380 (48)	380 (48)	82 (26)
Dyslipidemia; N (%)		528 (59)	432 (55)	337 (50)	157 (50)
Estimated glomerular filtration rate ≤60 ml/min/1.73m2; N (%)		25 (3)	93 (12)	197 (30)	146 (46)
Albuminuria (%)		8 (1)	13 (2)	6 (1)	6 (2)
Number of chronic medications at initiation; mean ± SD		3.4 ± 2.9	3.8 ± 2.8	5.1 ± 3.3	5.2 ± 3.6
Blood pressure-lowering medication at initiation; N (%)	No	469 (52)	307 (39)	160 (24)	89 (28)
	1 medication class	184 (21)	199 (25)	142 (21)	74 (23)
	2 medication classes	143 (16)	154 (19)	199 (30)	63 (20)
	3 or more medication classes	98 (11)	132 (17)	168 (25)	90 (28)
Treated with a lipid-lowering medication; N (%)		415 (46)	434 (55)	384 (57)	140 (44)
Initiated medication; N (%)	Metformin	797 (89)	705 (89)	587 (88)	239 (76)
	Sulphonyl urea	43 (5)	48 (6)	38 (6)	49 (16)
	α-glucosidase inhibitors	-	-	-	1 (0)
	Dipeptidyl Peptidase 4 (DDP-4) inhibitor	2 (0)	1 (0)	1 (0)	1 (0)
	Glucagon-like peptide-1 (GLP-1) agonist	2 (0)	-	-	-
	Sodium-glucose transport protein 2 (SGLT2) inhibitor	-	1 (0)	-	-
	Metformin + another medication	48 (5)	36 (4)	42 (6)	25 (8)
	Sulphonyl urea + another medication	2 (0)	1 (0)	1 (0)	1 (0)

Supplementary table 3: Characteristics of patients included in the glycosylated hemoglobin A1c (HbA1c) analyses per sex group

		Males	Females
Age group	< 60	503 (34)	391 (32)
	60-69	468 (32)	324 (27)
	70-79	359 (24)	310 (26)
	≥80	136 (9)	180 (15)
Glycated hemoglobin A1c at initiation in %; mean ± SD		7.8 ± 1.5	7.5 ± 1.4
Fasting glucose; mean ± SD		9.3 ± 3.1	8.9 ± 2.8
Diabetes duration; N (%)	0 – 1 years	547 (37)	420 (25)
	2 – 3 years	287 (20)	193 (16)
	4 – 5 years	248 (17)	234 (19)
	6 – 7 years	218 (15)	200 (17)
	8 – 9 years	166 (11)	158 (13)
Systolic blood pressure ≥140 mmHg; N (%)		568 (39)	487 (40)
Body mass index in kg/m^2; N (%)	< 24.9	175 (12)	170 (14)
	25 – 29.9	586 (40)	362 (30)
	≥ 30	678 (46)	631 (52)
Dyslipidemia; N (%)		765 (52)	689 (57)
Estimated glomerular filtration rate ≤ 60 ml/min/1.73m2; N (%)		222 (15)	239 (20)
Albuminuria (%)		26 (2)	7 (1)
Number of chronic medications at initiation; mean ± SD		3.8 ± 2.9	4.6 ± 3.3
Blood pressure-lowering treatment at initiation; N (%)	No	590 (40)	435 (36)
	1 medication class	321 (22)	278 (23)
	2 medication classes	288 (20)	271 (22)
	3 or more medication classes	267 (18)	221 (18)
Treated with a lipid-lowering drug; N (%)		775 (53)	589 (50)
Initiated medication; N (%)	Metformin	1,274 (87)	1,054 (87)
	Sulphonyl urea	94 (6)	84 (7)
	α-glucosidase inhibitors	-	1 (0)
	Dipeptidyl Peptidase 4 (DDP-4) inhibitor	2 (0)	3 (0)
	Glucagon-like peptide-1 (GLP-1) agonist	1 (0)	1 (0)
	Sodium-glucose transport protein 2 (SGLT2) inhibitor	1 (0)	-
	Metformin + another medication	92 (6)	59 (5)
	Sulphonyl urea + another medication	2 (0)	3 (0)

SUPPLEMENTARY MATERIAL 2 – SBP ANALYSES



Supplementary figure 2: Numbers of patients per calendar year in the systolic blood pressure (SBP) analyses based on the inclusion and exclusion criteria; GIANTT: Groningen Initiative to ANalyze Type 2 diabetes Treatment; T2D: type 2 diabetes

Supplementary table 4: Characteristics of patients included in the systolic blood pressure (SBP) analyses over the years

		2015	2016	2017	2018	2019	2020
Number of patients		419	315	353	377	392	272
Females; N (%)		223 (53)	152 (48)	154 (44)	170 (45)	188 (48)	124 (46)
Age in years; N (%)	<60	99 (24)	81 (26)	101 (29)	112 (30)	94 (24)	72 (26)
	60–69	128 (31)	96 (30)	100 (28)	111 (29)	124 (32)	91 (33)
	70–79	105 (25)	80 (25)	102 (29)	100 (27)	114 (29)	65 (24)
	≥80	87 (21)	58 (18)	50 (14)	54 (14)	60 (15)	44 (16)
Systolic BP at initiation in mmHg; mean ± SD		145 ± 21	147 ± 20	148 ± 21	146 ± 21	145 ± 20	149 ± 21
Diastolic BP at initiation in mmHg; mean ± SD		80 ± 13	81 ± 13	83 ± 13	81 ± 12	81 ± 12	83 ± 12
Diabetes duration; N (%)	0–1 year	69 (16)	35 (11)	17 (5)	57 (15)	55 (14)	40 (15)
	2–3 years	57 (14)	58 (18)	57 (16)	53 (14)	56 (14)	35 (13)
	4–5 years	57 (14)	41 (13)	55 (16)	48 (13)	42 (11)	33 (12)
	6–7 years	62 (15)	47 (15)	58 (16)	54 (14)	52 (13)	34 (13)
	8–9 years	61 (15)	32 (10)	44 (12)	36 (10)	51 (13)	26 (10)
	≥10 years	113 (27)	102 (32)	122 (35)	129 (34)	136 (35)	104 (38)
Glycated hemoglobin A1c < 7%; N (%)		207 (49)	162 (51)	187 (53)	183 (49)	209 (53)	124 (46)
Body mass index in kg/m^2; N (%)	<25	73 (17)	50 (16)	61 (17)	81 (21)	76 (19)	51 (19)
	25–29.9	168 (40)	123 (39)	154 (44)	129 (34)	152 (39)	97 (36)
	≥30	169 (40)	136 (43)	130 (37)	157 (42)	157 (40)	117 (43)
Dyslipidemia; N (%)		183 (54)	142 (58)	162 (58)	164 (50)	187 (56)	116 (51)
Estimated glomerular filtration rate ≤60 mL/min/1.73m^2; N (%)		76 (18)	69 (22)	41 (12)	69 (18)	70 (18)	43 (16)
Albuminuria; N (%)		11 (3)	14 (4)	10 (3)	14 (4)	12 (3)	7 (3)
Smoking; N (%)		80 (19)	53 (17)	50 (14)	79 (21)	66 (17)	43 (16)
History of cardiovascular disease; N (%)	Myocardial disease	60 (14)	34 (11)	30 (9)	32 (8)	33 (8)	24 (9)
	Heart failure	33 (8)	10 (3)	17 (5)	11 (3)	8 (2)	5 (2)
	Stroke	31 (7)	18 (6)	23 (7)	15 (4)	20 (5)	7 (3)

Supplementary table 4: Characteristics of patients included in the systolic blood pressure (SBP) analyses over the years (continued)

		2015	2016	2017	2018	2019	2020
Number of chronic medications at initiation; mean ± SD		4.0 ± 2.7	3.8 ± 2.9	3.7± 2.7	3.7 ± 2.8	3.7 ± 2.8	3.8 ± 2.8
Glucose-lowering medication at initiation; N (%)	No medication	147 (35)	100 (32)	118 (33)	141 (37)	165 (42)	89 (33)
	1 oral	153 (37)	115 (37)	125 (35)	131 (35)	129 (33)	83 (31)
	2 orals	64 (15)	65 (21)	52 (15)	41 (11)	46 (12)	50 (18)
	3 orals or more and/or insulin	55 (13)	35 (11)	58 (16)	64 (17)	52 (13)	50 (18)
Treated with lipid lowering medication; N (%)		215 (51)	176 (56)	184 (52)	175 (46)	195 (50)	128 (47)
Initiated medication class; N (%)	Renin-angiotensin-aldosterone system inhibitor	148 (35)	136 (43)	156 (44)	152 (40)	155 (40)	123 (45)
	Combination of antihypertensives	107 (26)	68 (22)	68 (19)	73 (19)	80 (20)	49 (18)
	Beta blocker	75 (18)	46 (15)	47 (13)	50 (13)	76 (19)	51 (19)
	Diuretic	54 (13)	38 (12)	50 (14)	61 (16)	37 (9)	20 (7)
	Calcium channel blocker	35 (8)	27 (9)	32 (9)	41 (11)	44 (11)	29 (11)

Supplementary table 5: Characteristics of patients included in the systolic blood pressure (SBP) analyses per age group

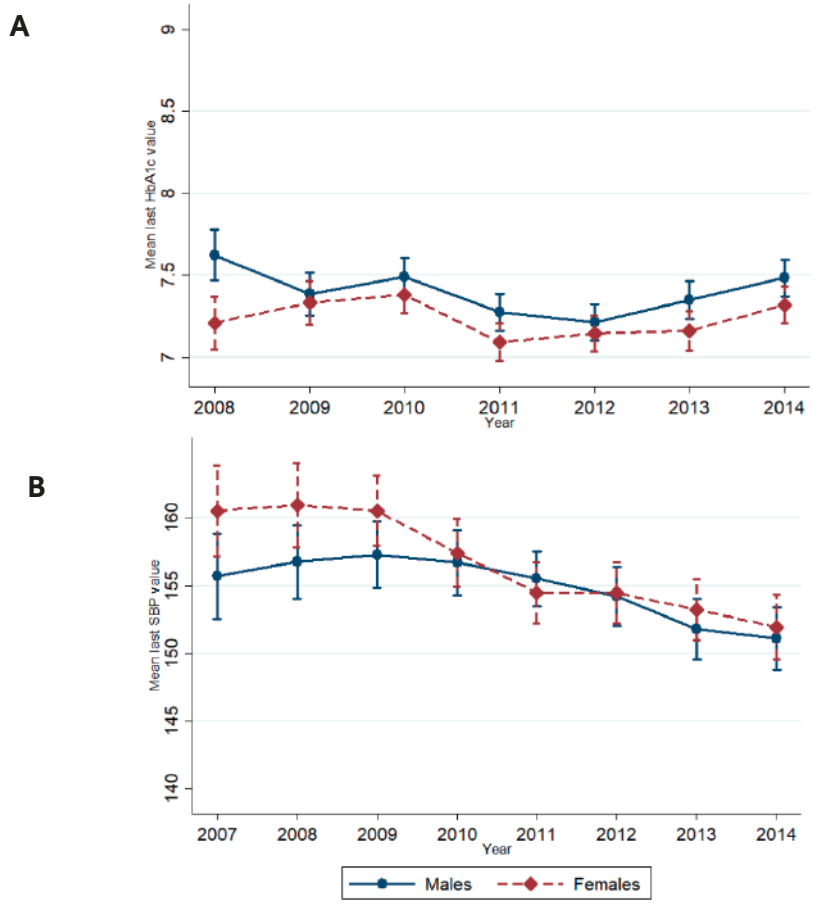
		<60 years	60-69 years	70-79 years	≥80 years
Females; N (%)		233 (42)	281 (43)	274 (48)	223 (63)
Systolic BP at initiation in mmHg; mean ± SD		146 ± 20	147 ± 21	147 ± 21	143 ± 21
Diastolic BP at initiation in mmHg; mean ± SD		88 ± 12	83 ± 12	78 ± 11	75 ± 12
Diabetes duration; N (%)	0 – 1 years	117 (21)	80 (12)	52 (9)	24 (7)
	2 – 3 years	123 (22)	94 (14)	64 (11)	35 (10)
	4 – 5 years	82 (15)	95 (15)	65 (11)	34 (10)
	6 – 7 years	85 (15)	109 (17)	73 (13)	40 (11)
	8 – 9 years	64 (11)	74 (11)	72 (13)	40 (11)
	≥ 10 years	88 (16)	198 (30)	240 (42)	180 (51)
Glycated hemoglobin A1c < 7%; N (%)		264 (47)	335 (52)	294 (52)	179 (51)
Body mass index in kg/m^2; N (%)	< 24.9	41 (7)	119 (18)	120 (21)	112 (32)
	25 – 29.9	164 (29)	263 (40)	246 (43)	150 (42)
	≥ 30	339 (60)	256 (39)	188 (33)	83 (24)
Dyslipidemia; N (%)		270 (48)	306 (47)	245 (43)	133 (38)
Estimated glomerular filtration rate ≤60 ml/min/1.73m2; N (%)		17 (3)	51 (8)	124 (22)	176 (50)
Albuminuria (%)		16 (3)	18 (3)	16 (3)	18 (5)
Smoking; N (%)		139 (25)	129 (20)	80 (14)	23 (7)
History of cardiovascular disease; N (%)	Myocardial disease[1]	21 (4)	61 (9)	71 (13)	60 (17)
	Heart failure[2]	3 (1)	13 (2)	24 (4)	44 (12)
	Stroke[3]	8 (1)	25 (4)	42 (7)	39 (11)
Number of chronic medications at initiation; mean ± SD		3.8 ± 2.6	3.7 ± 2.8	3.8 ± 2.8	4.4 ± 3.0
Glucose-lowering medication at initiation; N (%)	No	183 (33)	225 (35)	208 (37)	144 (41)
	1 oral	192 (34)	231 (26)	201 (36)	112 (32)
	2 orals	87 (16)	112 (17)	77 (14)	42 (12)
	3 orals or more and/or insulin	97 (17)	82 (13)	80 (14)	55 (16)
Treated with lipid-lowering medication; N (%)		289 (52)	375 (58)	286 (51)	123 (35)
Initiated medication class; N (%)	Renin-angiotensin-aldosterone system inhibitor	298 (62)	284 (54)	197 (45)	91 (38)
	Combination of antihypertensives	79 (14)	121 (19)	132 (23)	113 (32)
	Beta blocker	62 (13)	90 (17)	115 (27)	78 (33)
	Diuretic	75 (16)	90 (17)	52 (12)	43 (18)
	Calcium channel blocker	45 (9)	65 (12)	70 (16)	28 (12)

Supplementary table 6: Characteristics of patients included in the systolic blood pressure (SBP) analyses per sex group

		Males	Females
Age group	<60	326 (29)	233 (23)
	60-69	369 (33)	281 (28)
	70-79	292 (26)	274 (27)
	≥80	130 (12)	223 (23)
Systolic BP at initiation in mmHg; mean ± SD		147 ± 21	146 ± 21
Diastolic BP at initiation in mmHg; mean ± SD		82 ± 13	80 ± 12
Diabetes duration; N (%)	0 – 1 years	161 (14)	112 (11)
	2 – 3 years	185 (17)	131 (13)
	4 – 5 years	131 (12)	145 (14)
	6 – 7 years	159 (14)	148 (15)
	8 – 9 years	126 (11)	124 (12)
	≥ 10 years	355 (32)	351 (35)
Glycated hemoglobin A1c < 7%; N (%)		544 (49)	528 (52)
Body mass index in kg/m^2; N (%)	< 24.9	193 (17)	199 (20)
	25 – 29.9	487 (44)	336 (33)
	≥ 30	410 (37)	456 (45)
Dyslipidemia; N (%)		488 (44)	466 (46)
Estimated glomerular filtration rate ≤60 ml/min/1.73m2; N (%)		170 (15)	198 (20)
Albuminuria (%)		46 (4)	22 (2)
Smoking; N (%)		205 (18)	166 (16)
History of cardiovascular disease; N (%)	Myocardial disease[1]	144 (13)	69 (7)
	Heart failure[2]	40 (4)	44 (4)
	Stroke[3]	54 (5)	60 (6)
Number of chronic medications at initiation; mean ± SD		3.5 ± 2.6	4.1 ± 2.9
Glucose-lowering medication at initiation; N (%)	No medication	374 (33)	386 (38)
	1 oral	396 (35)	340 (34)
	2 orals	191 (17)	127 (13)
	3 orals or more and/or insulin	156 (14)	158 (16)
Treated with a lipid-lowering medication; N (%)		602 (54)	471 (47)
Initiated medication class; N (%)	Renin-angiotensin-aldosterone system inhibitor	512 (57)	358 (46)
	Combination of antihypertensives	218 (20)	227 (22)
	Beta blocker	180 (20)	165 (21)
	Diuretic	101 (11)	159 (20)
	Calcium channel blocker	106 (12)	102 (13)

SUPPLEMENTARY MATERIAL 3 – SEX DIFFERENCES IN THE YEARS 2007 TO 2014

Ambroz M, de Vries ST, Hoogenberg K, Denig P. Trends in HbA1c thresholds for initiation of hypoglycemic agents: Impact of changed recommendations for older and frail patients. Pharmcoepidemiology and Drug Safety. 2021;30(1):37-44.
Ambroz M, de Vries ST, Sidorenkov G, Hoogenberg K, Denig P. Changes in blood pressure thresholds for initiating antihypertensive medication in patients with diabetes: a repeated cross-sectional study focusing on the impact of age and frailty. BMJ Open. 2020;10(9):1-8. e037694.



Supplementary figure 3: Mean last (a) glycated hemoglobin A1c (HbA1c) levels before/at initiation of glucose-lowering medication between 2008 and 2014 and (b) systolic blood pressure (SBP) levels before/at initiation of blood pressure lowering medication between 2007 and 2014. Mean levels are adjusted for confounders and presented with 95% confidence intervals.

5

Sex disparities in medication prescribing among patients with type 2 diabetes mellitus managed in primary care

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Diabet Med. 2022 Oct 24;e14987

ABSTRACT

Background

Sex differences in clinical outcomes have been observed for patients with type 2 diabetes mellitus (T2DM). These could be related to sex disparities in treatment.

Objectives

To determine whether there are sex disparities in medication prescribing among patients with T2DM.

Methods

A cohort study was conducted using the Groningen Initiative to ANalyze Type 2 diabetes Treatment (GIANTT) database, which includes data of primary care patients with T2DM from the north of the Netherlands. Data on demographics, physical examinations, laboratory measurements and prescribing were extracted. A set of validated prescribing quality indicators assessing the prevalence, start, intensification and safety of glucose-, lipid-, blood pressure- and albuminuria-lowering medication was applied for the calendar year 2019. Univariate logistic regression analyses were conducted.

Results

We included 10,456 patients (47% females). Females were less often treated with metformin (81.7% vs. 86.5%; OR 0.70, 95%CI 0.61-0.80), and were less often prescribed a renin angiotensin aldosterone inhibitor (RAAS-i) when treated with multiple blood pressure-lowering medicines (81.9% vs. 89.3%; OR 0.55, 95%CI 0.46-0.64) or when having albuminuria (74.7% vs. 82.1%; OR 0.64, 95%CI 0.49-0.85) than males. Statin treatment was less frequently started (19.7% vs. 24.7%; OR 0.75, 95%CI 0.58-0.96) and prescribed (58.7% vs. 63.9%; OR 0.80, 95%CI 0.73-0.89) in females. There were no differences in starting and intensifying glucose-, blood pressure- and albuminuria-lowering medication.

Conclusions

Sex disparities in medication prescribing among T2DM patients were seen, including less starting with statins and potential undertreatment with RAAS-i in females. Such disparities may partly explain higher excess risks for cardiovascular and renal complications associated with diabetes observed in females.

INTRODUCTION

People with type 2 diabetes mellitus (T2DM) have an increased risk of cardiovascular and renal complications. Therefore, guidelines for the treatment of diabetes recommend monitoring risk factors, such as glucose, blood pressure, lipid, and albuminuria levels, and to prescribe medication treatment in case specified targets are not reached with lifestyle changes (1, 2). The guidelines do not differentiate between females and males despite findings of sex differences in risks for cardiovascular and renal complications. Meta-analyses have shown that the excess risk of stroke, coronary heart disease and end-stage renal disease associated with diabetes is larger in females than males (3-5). This raises the question whether there are sex disparities in the quality of diabetes treatment.

Whether clinicians provide care in accordance with the guidelines is evaluated by quality indicators. Most quality indicators for diabetes care focus on monitoring risk factors (process indicators) and achieving recommended targets (outcome indicators) (6, 7). A recent review on sex differences in diabetes care showed mixed findings regarding disparities in quality indicators (8). Several of the included studies showed that females and males reached glycosylated haemoglobin A1c (HbA1c) and blood pressure targets to a similar extent, whereas for low-density lipoprotein cholesterol (LDL-c) females reached the target levels less often than males. Few studies included in this review assessed whether there were sex differences in receiving treatment with inconsistent results and none assessed whether medication treatment was prescribed when indicated. For example, in a Dutch primary care cohort of T2DM patients it was found that females more often used blood pressure-lowering medication and less often used lipid-lowering medication, but this was not assessed in relation to the need for such medication (9).

Previously, a set of twenty prescribing quality indicators (PQIs) for the treatment of T2DM patients has been developed and validated (10). The PQIs were derived from evidence-based guideline recommendations and focus on the prescribing of glucose-, lipid-, blood pressure- and albuminuria-lowering medication. The indicators cover a range of quality aspects and assess (a) whether and which medication is prescribed (prevalent and first choice medication), (b) timely start and intensification of medication when recommended targets are not reached (clinical action), and (c) potential inappropriate prescribing and overtreatment (medication safety). Clinical action indicators aim to assess therapeutic inertia, which is seen as a major concern in patients with T2DM (11). They have been associated with better outcomes in patients with T2DM and are considered important for assessing the quality of medication treatment (7, 12). Indicators focusing on medication safety have been associated with poorer

outcomes, and can be particularly relevant for females, who appear more vulnerable for adverse drug reactions (ADRs) (13, 14).

The aim of the current study was to determine whether there are sex disparities in medication prescribing among patients with T2DM managed in primary care evaluated by a comprehensive set of PQIs.

MATERIALS AND METHODS

Study design and population

A cohort study was conducted using the Groningen Initiative to ANalyze Type 2 diabetes Treatment (GIANTT; www.giantt.nl) database (15). The GIANTT database consists of anonymous data from electronic medical records of a dynamic cohort of more than 50,000 patients with T2DM in the northern part of the Netherlands. We evaluated sex disparities in prescribing for the year 2019, which was the most recent calendar year with representative data available. Included were patients aged ≥18 years with a valid diagnosis date of T2DM, treated by a general practitioner, included in the database for the whole calendar year, and who had at least one year of medical history. An exemption letter for full ethical approval was obtained from the University Medical Center Groningen Medical Ethics Review Board (reference number M20.261871).

Outcomes

The quality of medication prescribing was assessed using a set of twenty PQIs (10). The PQIs focus on (a) prevalent and first choice medication, (b) clinical action, and (c) medication safety (Table 1). For calculating the PQIs under (a) and (c), data from the calendar year 2019 were used, whereas for PQIs under (b) also data from the calendar year 2018 were needed (Table 1).

Table 1. Prescribing quality indicators (PQIs) for patients with type 2 diabetes mellitus (T2DM) (10)

Prevalent and first choice medication	Short name
% of patients* treated with glucose-lowering medication that is prescribed metformin	Metformin prescribed
% of patients* treated with two non-insulin glucose-lowering medicines that is prescribed a combination of metformin and an SU-derivative	Metformin with SU prescribed
% of patients between 55 and 80 years that is prescribed a statin	Statin prescribed
% of patients treated with two or more blood pressure-lowering medicines that is prescribed an ACE-i or ARB (RAAS-i)	RAAS-i prescribed for blood pressure
% of patients with albuminuria treated with medication that is prescribed a RAAS-i (ACE-i or ARB)	RAAS-i prescribed for albuminuria
% of patients* starting with oral glucose-lowering medication that started with metformin	Metformin first choice

Table 1. Prescribing quality indicators (PQIs) for patients with type 2 diabetes mellitus (T2DM) (10) (continued)

Prevalent and first choice medication (continued)	**Short name**
% of patients starting with an SU-derivative that started with gliclazide	Gliclazide first choice
% of patients starting with RAAS-i that started with an ACE-i	ACE-i first choice
Clinical action	
% of patients between 18 and 70 years with an HbA1c level >53 mmol/mol (7.0 %) in the previous year, that started with glucose-lowering medication or reached HbA1c target level ≤53 mmol/mol (7.0 %)	Glucose-lowering start
% of patients between 18 and 70 years treated with monotherapy metformin and an HbA1c level >53 mmol/mol (7.0 %) in the previous year, that intensified glucose-lowering medication or reached HbA1c target level ≤53 mmol/mol (7.0 %)	Glucose-lowering intensification
% of patients between 18 and 70 years treated with two or more non-insulin glucose-lowering medicines and an HbA1c level >53 mmol/mol (7.0 %) in the previous year, that started with insulin or reached HbA1c target level ≤53 mmol/mol (7.0 %)	Insulin start
% of patients between 18 and 80 years with an LDL-c level >2.5 mmol/l in the previous year, that started with a statin or reached LDL-c target level ≤2.5 mmol/l	Statin start
% of patients between 18 and 80 years treated with simvastatin and an LDL-c level >2.5 mmol/l in the previous year, that switched to atorvastatin or rosuvastatin or reached LDL-c target level ≤2.5 mmol/l	Statin intensification
% of patients between 18 and 70 years with an SBP >140 mmHg in the previous year, that started with blood pressure-lowering medication or reached SBP target level ≤140 mmHg	Blood pressure-lowering start
% of patients between 18 and 70 years treated with monotherapy blood pressure-lowering medication and an SBP >140 mmHg in the previous year, that intensified blood pressure-lowering medication or reached SBP target level ≤140 mmHg	Blood pressure-lowering intensification
% of patients with T2DM between 18 and 70 years with albuminuria in the previous year, that started with an ACE-i or ARB or that returned to normo-albuminuria	RAAS-i start with albuminuria
Medication safety	
% of patients treated with an SU-derivative that is prescribed glibenclamide	Glibenclamide choice
% of patients with an eGFR <30 mL/min/1.73m^2 that is prescribed metformin	Metformin with poor renal function
% of patients 80 years or older with an HbA1c level <53 mmol/mol (7.0 %) that is prescribed two or more glucose-lowering medicines	Glucose-lowering overtreatment elderly
% of patients treated with RAAS-i that is prescribed a combination of an ACE-i and ARB (dual RAAS blockage)	Dual RAAS-i blockage

Abbreviations: T2DM = type 2 diabetes mellitus; ACE-i = angiotensin-converting-enzyme inhibitor; ARB = angiotensin receptor blocker; HbA1c = glycosylated haemoglobin A1c; SBP = systolic blood pressure; LDL-c = low density lipoprotein cholesterol; eGFR = estimated glomerular filtration rate; RAAS-i = renin-angiotensin-aldosterone system inhibitor; SU-derivative = sulfonylurea derivative. Albuminuria is defined as albumin creatinine ratio ≥2.5 mg/mmol for males and ≥3.5 for females or albumin in 24h urine ≥30 mg. * excluding patients with eGFR<30 mL/min/1.73m^2

The presence of prescriptions for metformin (Anatomical Therapeutic Chemical (ATC) code: A10BA02), sulfonylurea (SU) derivatives (ATC code: A10BB), all non-insulin glucose-lowering medication (ATC code: A10B), insulins (ATC code: A10A), simvastatin (ATC code: C10AA01), atorvastatin (ATC code: C10AA05), rosuvastatin (ATC code: C10AA07), all statins (ATC code: C10AA), angiotensin-converting enzyme inhibitors (ACE-i, ATC code: C09A), angiotensin II receptor blockers (ARB, ATC code: C09C), all renin-angiotensin-aldosterone system inhibitors (RAAS-i, ATC code: C09), calcium channel blockers (ATC code: C08), beta blockers (ATC code: C07), and diuretics (ATC code: C03) were assessed in the last four months of the calendar year. Furthermore, the most recent values of HbA1c, systolic blood pressure (SBP), LDL-c, albumin/creatinine ratio (ACR), albumin in 24h urine, and estimated glomerular filtration rate (eGFR) in the calendar year were included for calculating the PQIs.

Explanatory variable

Sex of the patients as registered in the GIANTT database (female or male) was the explanatory variable.

Other background variables

Age, T2DM duration, body mass index (BMI), presence or history of cardiovascular disease (CVD), and the use of relevant medication classes were included as background variables. Age and diabetes duration were assessed on January 1st, 2019. BMI was calculated using the most recent value for height until December 31st, 2019, and the most recent value for weight in the period of January 1st, 2015, to December 31st, 2019. We used BMI as entered in the database when weight and/or height were not available. Presence or history of CVD included any record of angina pectoris, acute myocardial infarction, transient ischemic attack, stroke, atherosclerosis, other ischemic heart diseases and peripheral arterial diseases, abdominal aortic aneurysm, coronary or peripheral percutaneous transluminal angioplasty, and/or bypass in GIANTT until December 31st, 2019. For all diabetes related medication, including also dipeptidyl peptidase 4 (DDP-4) inhibitors (ATC code: A10BH), glucagon-like peptide-1 (GLP-1) analogues (ATC code: A10BJ) and sodium-glucose co-transporter 2 (SGLT2) inhibitors (ATC code: A10BK), the presence of prescriptions were assessed in the last four months of the calendar year, which is the same period as used for the medication included in the study outcomes.

Statistical analyses

Patient characteristics are presented as mean with standard deviation (SD), median with interquartile range (IQR), or percentages for respectively normally distributed, non-normally distributed, and categorical variables. Sex differences in patient charac-

teristics were tested using respectively independent-samples t-tests, Mann-Whitney U tests, and Chi-Squared tests. Differences in PQI scores between females and males were assessed using a univariate logistic regression analysis. Odd Ratios (ORs) with 95% Confidence Intervals (CIs) are presented and differences with a P-value <0.05 were considered statistically significant. Although the PQIs were developed for the whole population with T2DM without the need to adjust for confounders, several patient characteristics can still have a justifiable influence on the decision to (not) prescribe a certain medication as recommended in general, e.g., due to contraindications or specific needs for such medication. We therefore conducted a sensitivity analysis adjusting the analyses of the PQIs assessing (a) prevalent and first choice medication and (b) clinical action for age, eGFR and presence or history of CVD. Seventeen percent of patients had a missing value for eGFR, which we imputed using multiple imputation by chained equations. Although the PQIs were developed around 2014, they were still appropriate for the treatment recommendations in the diabetes guideline updates for the Netherlands up to the year 2021. Nevertheless, we conducted additional analyses using the calendar years 2012, the year for which the developed PQIs have been validated (10), and 2017, the year before the diabetes guideline was updated in the Netherlands (2), to assess the robustness of the results over time. All analyses were conducted using Stata version 14 (Stata Corp., College Station, TX).

RESULTS

Baseline characteristics

After excluding 17 patients younger than 18 years, 73 patients without a date of T2DM diagnosis, and 79 patients with insufficient medical history, we included 10,456 patients of which 4,955 (47%) were females. Females were older, had a longer diabetes duration, a higher BMI, more often an LDL-c level >2.5 mmol/L and a lower eGFR level (Table 2). Conversely, males had more often micro/macro-albuminuria and a presence or history of CVD than females. Regarding the crude percentages of patients receiving medication treatment, the largest differences were seen for statins (53% in females vs. 60% in males), diuretics (42% vs. 35%), RAAS-i (50% vs. 56%) and metformin (54% vs. 59%). The use of newer diabetes medication classes, such as SGLT2 inhibitors, was low (Table 2).

Quality of medication treatment

Statistically significant differences were seen between females and males in five of the twenty PQIs (Figure 1), where females less often received recommended medication treatment than males. Regarding prevalent and first choice medication, females

were less often prescribed metformin when treated with glucose-lowering medication (metformin prescribed: 81.7% vs. 86.5%, OR 0.70, 95% CI 0.61-0.80) and prescribed a statin when commonly indicated compared to males (statin prescribed when aged 55-80 years: 58.7% vs. 63.9%, OR 0.80, 95% CI 0.73-0.89). Furthermore, females were less often treated with a RAAS-i when treated with multiple blood pressure-lowering medicines (RAAS-i prescribed for blood pressure: 81.9% vs. 89.3%, OR 0.55, 95% CI 0.46-0.64) and prescribed RAAS-i when having albuminuria (RAAS-i prescribed for albuminuria: 74.7% vs. 82.1%, OR 0.64, 95% CI 0.49-0.85). There were no sex differences in the prescribing of metformin and SU-derivative in combination or in first-choice medication, such as choosing gliclazide when initiating an SU-derivative or choosing an ACE-i when initiating RAAS-i treatment.

Table 2. Background characteristics and prescribed medication[a] for all included patients and by sex

	Overall (N=10,456)	Males (n=5,501)	Females (n=4,955)	P-value
Age (years), mean ± SD	69 ± 12	68 ± 12	70 ± 13	<0.001
T2DM duration (years), median [IQR][b]	8.7 [4.8-13.6]	8.5 [4.7-13.2]	9.0 [5.1-14.0]	<0.001
BMI (kg/m²), mean ± SD	30.0 ± 5.6	29.4 ± 5.0	30.5 ± 6.2	<0.001
missing	996 (10)	540 (10)	456 (9)	
SBP >140 mmHg, n (%)	2,853 (27)	1,485 (27)	1,368 (28)	0.870
missing	1,655 (16)	909 (17)	746 (15)	
HbA1c >53 mmol/mol (7.0 %), n (%)	4,230 (40)	2,225 (40)	2,005 (40)	0.197
missing	1,530 (15)	870 (16)	660 (13)	
LDL-c >2.5 mmol/L, n (%)	3,751 (36)	1,768 (32)	1,983 (40)	<0.001
missing	2,556 (24)	1,365 (25)	1,191 (24)	
Albuminuria[c], n (%)	1,495 (14)	997 (18)	498 (10)	<0.001
missing	3,070 (29)	1,616 (29)	1,454 (29)	
eGFR (ml/min/1.73m²), mean ± SD	73 ± 20	74 ± 20	72 ± 21	<0.001
missing	1,823 (17)	1,054 (19)	769 (16)	
CVD, n (%)[d]	3,246 (31)	1,800 (33)	1,446 (29)	<0.001
Glucose-lowering medication	7,252 (69)	3,903 (71)	3,349 (68)	0.001
1	4,097	2,129	1,968	
2	2,644	1,477	1,167	
≥3	511	297	214	
Insulin	1,940 (19)	989 (18)	951 (20)	0.111
Metformin	5,909 (57)	3,255 (59)	2,654 (54)	<0.001
SU-derivatives	2,655 (25)	1,490 (27)	1,165 (24)	<0.001
DPP-4 inhibitors	410 (4)	240 (4)	170 (3)	0.014

Table 2. Background characteristics and prescribed medication[a] for all included patients and by sex (continued)

	Overall (N=10,456)	Males (n=5,501)	Females (n=4,955)	P-value
GLP-1 analogues	279 (3)	119 (2)	160 (3)	0.001
SGLT2 inhibitors	128 (1)	73 (1)	55 (1)	0.314
Blood pressure-lowering medication	7,329 (70)	3,833 (72)	3,496 (71)	0.610
1	2,148	1,134	1,014	
2	2,440	1,250	1,190	
≥3	2,741	1,449	1,292	
RAAS inhibitors	5,539 (53)	3,062 (56)	2,477 (50)	<0.001
Calcium channel blockers	2,526 (24)	1,399 (25)	1,127 (23)	0.001
Beta blockers	3,850 (37)	1,962 (36)	1,888 (38)	0.010
Diuretics	3,989 (38)	1,908 (35)	2,081 (42)	<0.001
Statins	5,939 (57)	3,317 (60)	2,622 (53)	<0.001

Abbreviations: T2DM = type 2 diabetes mellitus; BMI = body mass index; SBP = systolic blood pressure; HbA1c = glycosylated haemoglobin A1c; LDL-c = low density lipoprotein cholesterol; eGFR = estimated glomerular filtration rate; CVD = cardiovascular disease; SU = sulphonyl urea; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon like peptide-1; SGLT2 = sodium-glucose cotransporter-2; RAAS = renin-angiotensin aldosterone system. *Note:* [a] Prescribed medication in the last 4 months of 2019. [b] Diabetes duration were assessed on January 1st, 2019. [c] Albuminuria was defined as albumin creatinine ratio ≥2.5 mg/mmol for males and ≥3.5 for females or albumin in 24h urine ≥30 mg. [d] CVD includes any record of a CVD (angina pectoris, acute myocardial infarction, transient ischemic attack, stroke, atherosclerosis, other ischemic heart diseases and peripheral arterial diseases, abdominal aortic aneurysm, percutaneous transluminal (coronary) angioplasty, and peripheral or coronary bypass) in GIANTT until December 31st, 2019. P-values were obtained via independent t-tests (age and BMI), Mann-Whitney U test (T2DM duration), and Chi Square tests (SBP, HbA1c, LDL-c, albuminuria, and all prescribed medication).

With respect to clinical action, statin treatment was less often started in females with elevated LDL-c lev-els compared to males (statin start: 19.7% vs. 24.7%, OR 0.75, 95% CI 0.58– 0.96). Clinical action regarding the intensification of statins and the start or intensifica-tion of glucose- lowering, blood pressure- lowering and albuminuria- lowering medication was similar for females and males with elevated LDL-c, HbA1c, SBP or albumin-uria levels (Figure 1).

Finally, no sex disparities were seen in any of the four indicators related to medication safety (Figure 1).

Sensitivity analyses

Adjusting for age, eGFR and CVD revealed similar results as the univariate analyses (Supplementary Figure S1).

In the univariate analyses for the year 2012 and the year 2017, respectively 26,093 patients and 13,271 patients were included (51% females and 48% females; Supplementary Table S1 and Supplementary Table S2). The patient characteristics in these years were similar to those included in the main analysis. These analyses

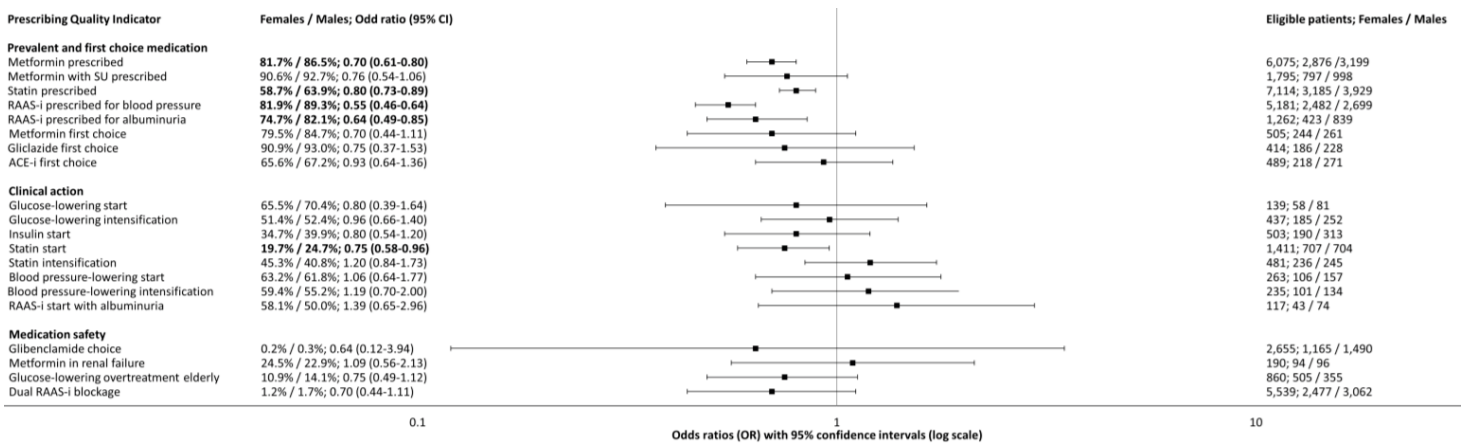

Figure 1. Univariate analyses of sex disparities in medication prescribing in 2019. Odds ratios with 95% confidence intervals (log scale). *Abbreviations:* SU; sulfonylurea, RAAS-i; renin-angiotensin aldosterone system inhibitor, ACE-i; angiotensin-converting-enzyme inhibitor OR; odds ratio, CI; confidence interval. *Note:* P<0.05 between females and males is marked bold. ORs below 1 indicate lower scores for females. The number of eligible patients are patients for whom the prescribing quality indicator could be calculated and applied.

showed statistically significant sex differences in the same PQIs as observed in the main analyses using data from the year 2019 (Supplementary Figures S2 and S3) but showed some additional sex disparities.

In the year 2012 (Supplementary Figure S2), females were less often prescribed a combination of metformin and an SU-derivative (metformin with SU-derivative prescribed: 85.6% vs. 88.3%, OR 0.79, 95% CI 0.68-0.93), less often started with an ACE-i when RAAS-i treatment was initiated (ACE-i first choice: 67.0% vs. 74.4%, OR 0.74, 95% CI 0.57-0.95) and less often received intensification of statin treatment with elevated LDL-c levels (statin intensification: 43.8% vs. 48.2%, OR 0.84, 95% CI 0.71-0.99).

In the year 2017 (Supplementary Figure S3), females less often started with an ACE-i when RAAS-i treatment was initiated (ACE-i first choice: 63.3% vs.76.4%, OR 0.53, 95% CI 0.38-0.74), elderly females were less often overtreated with glucose-lowering medication when compared to elderly males (glucose-lowering overtreatment elderly: 10.3% vs. 14.5%, OR 0.67, 95% CI 0.47-0.97) and females were less often prescribed a combination of an ACE-i and an ARB (dual RAAS-i blockage: 1.5% vs. 2.3%, OR 0.63, 95% CI 0.45-0.89).

DISCUSSION

This study illustrates that there are disparities in the medication prescribing between females and males with T2DM. Differences in prevalent treatment were seen for metformin, RAAS-i treatment, and statins, where females were less likely to receive such medication. There were no consistent sex differences in first choice medication. Regarding clinical action, starting statin treatment when needed was less likely for females as compared to males. Furthermore, there were no differences regarding starting or intensifying glucose-, blood pressure- and albuminuria-lowering medication when needed. Regarding medication safety, no statistically significant differences between females and males were observed. These findings were consistent over the past decade.

Our finding that there were no differences in starting and intensifying glucose-lowering and blood pressure-lowering treatment is in line with previous results reported in a review showing that risk factor control for HbA1c and SBP were often similar for both sexes (8). Also, it is consistent with a study showing no sex differences for no glucose- or no blood pressure-lowering medication in the presence of an elevated HbA1c or SBP level, respectively (16). However, earlier studies did indicate that female patients in general and female patients with high CVD risk scores were more likely to receive blood pressure-lowering treatment than male patients (9, 16).

These were both cross-sectional studies, where there is a risk of reverse causality, whereas we assessed actual treatment actions after having a high risk factor level. The sex differences we observed in prevalent use of recommended agents, including metformin and RAAS-i, remained after adjusting for age, eGFR and history or presence of CVD, meaning that sex differences in these characteristics do not explain this finding. They might, however, be explained by other differences in unmeasured characteristics, such as a patient's hypoglycaemia risk, other side effects, fear of side effects, or individual preferences. Particularly females are known to experience ADRs more often than males (13, 17, 18), which has also been observed for metformin and RAAS-i (19, 20). Our finding of no sex difference in metformin as first step treatment but less prevalent metformin use among females suggest that females have more tolerability issues with metformin, leading to more switching to other drugs. Less prescribing of RAAS-i in case of albuminuria was also not related to the start of such treatment but only seen regarding prevalent treatment both in patients with albuminuria and those using multiple blood pressure-lowering medication. Again, this may be explained with females experiencing more problems with RAAS-i than males.

The finding that statins were less often started and prescribed in general among females with elevated LDL-c levels is largely consistent with previous findings. It has been shown that females with diabetes less often use lipid-lowering medication (9) and are less likely to achieve risk factor control for LDL-c (8, 16). In a previous study, similar sex differences in lipid-lowering medication in the presence of elevated LDL-c levels and/or high CVD risk scores were only observed among patients in secondary or tertiary care (16). Our study indicates that this problem of insufficient LDL-c control was partly due to clinical inertia. Clinicians might be more hesitant to start statins in females because they are older or more frail (21), but adjusting for possible confounders did not change our finding. In people aged over 80 years in the United Kingdom, the rate of statin initiation was slightly lower in females than males (21). The PQI we used for assessing the start of statins, however, was restricted to patients younger than 80 years of age. Again, sex differences in expected or experienced ADRs could have played a role in our findings related to statin treatment. It has been observed that females more often start with a low dose statin-treatment than males (22), which might be due to more concerns about potential ADRs in females. Also, previous studies have shown that females more often stop a statin because of ADRs (23, 24). Since the need to prescribe a statin is higher when a patient has a history of CVD (25), we adjusted the analysis for the history or presence of CVD. This did not change the results, making this an unlikely explanation for the observed differences.

Regarding medication safety, we observed relatively high levels of metformin prescribed in patients with poor renal function and potential overtreatment with glucose-lowering medication among elderly but no significant differences between

the sexes. The use of metformin in people with poor renal function has been a matter of debate and low doses of metformin are now considered appropriate (26). Potential overtreatment with glucose-lowering medication and the need for deprescribing has received quite some attention in the last decade (27). Apparently, this has not yet resulted in low levels of potential overtreatment.

Strengths and limitations

A strength of this study is the use of previously developed and validated PQIs to assess the quality of medication treatment. Furthermore, we used longitudinal data from a large real-world cohort of patients with T2DM from primary care in the north of the Netherlands, taking the dynamics of starting and intensifying medication into account. We used data from one calendar year and repeated our analysis in two other years to test the robustness of our findings.

It should be noted that the GIANTT database consists of a dynamic cohort of patients and general practices. Therefore, variations in findings between the years can be caused by differences in the included patients and general practices. Characteristics of the included patients were relatively similar between the years and the number of practices ranged from 76 to 189 in the included years. Furthermore, this study included only patients with T2DM managed in primary care, so the results may not be generalisable to people managed in other settings. As with any study making use of data collected in routine care, there were variables with missing values. There were some differences in the percentages of missing values between males and females, with males having slightly more missing eGFR and HbA1c values. The percentages of missing values were different in the other years and since the analyses of the other years showed similar results, we believe the missingness did not influence our results greatly.

In our sensitivity analyses, we only adjusted for those patient characteristics that might have a justifiable influence on certain prescribing decisions, although most were already incorporated in the related PQI definitions. Further adjustment can obscure meaningful sex differences in the PQI scores. In addition, we conducted some post-hoc subgroup analyses (Supplementary table S3). The subgroup analyses revealed that the point estimates for most of the associations remained in the same direction but the significance was sometimes lost in one subgroup (Supplementary table S3). In the age group <60 years, however, the point estimates seemed to increase for all clinical action indicators and a significant difference was observed regarding more blood pressure-lowering medication intensification among younger females when compared to younger males.

There were some minor changes in the guideline recommendations related to the target levels for older and frail patients between 2012 and 2019 (2, 28-30), but given

the age restrictions in the related PQIs they were still valid for our study period. Other changes in treatment recommendations have been made after our study period in 2021, particularly regarding the use of novel diabetes agents in patients with high cardiovascular risk. The use of these agents was very limited in our primary care cohort in 2019.

Implications

Previous studies have been inconclusive about sex differences in diabetes management, but these studies were limited by focusing on risk factor control and prevalent use of medication among T2DM patients. Our study adds to this by identifying sex disparities with respect to specific aspects of the quality of medication prescribing. Given the previously observed sex differences in excess risks for cardiovascular and renal complications, it is of concern that females less often start guideline-recommended lipid-lowering treatment and also less often receive treatment with RAAS-i. Further studies are needed to establish whether this is due to a higher vulnerability for ADRs of these drugs among females. More efforts may be needed to tailor both lipid- and albuminuria-lowering treatment and manage possible ADRs in females with T2DM. Regarding the choice of medication, there can be valid reasons for not prescribing the medication of first choice. Our study shows that the initial choice of medication treatment was similar for females and males, and disparities mainly occur later in the treatment course. To some extent this could reflect treatment choices based on individual patient characteristics, which can differ between the sexes. Finally, our study illustrates that a comprehensive set of PQIs can offer meaningful insights in sex differences in the quality of prescribing among patients with T2DM. Regarding starting and intensifying glucose-lowering and blood pressure-lowering medication and medication safety issues, no significant sex differences were encountered.

Conclusions

Sex disparities in medication prescribing among T2DM patients were shown, including less starting with statins and potential undertreatment with RAAS-i in females. Such disparities may in part explain the excess risk for cardiovascular and renal complications associated with T2D previously observed in females.

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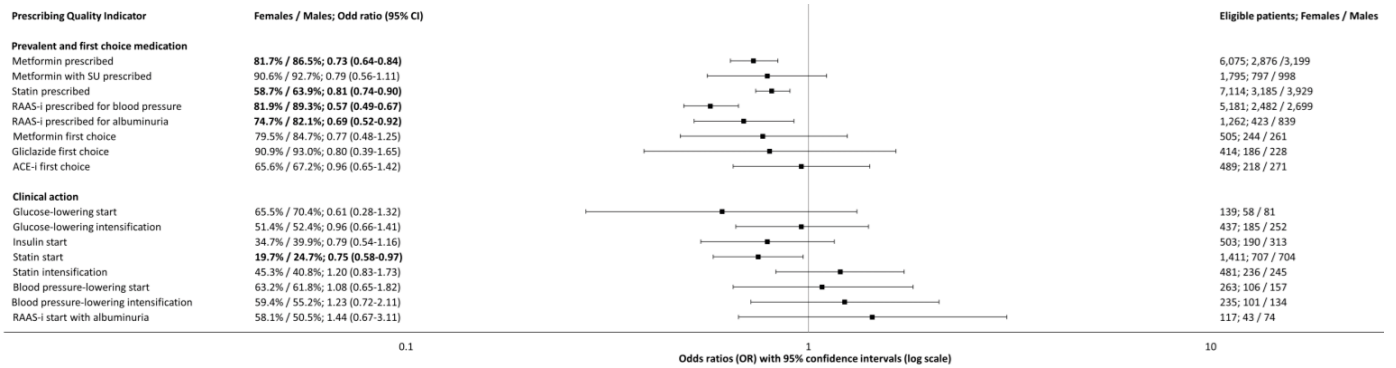


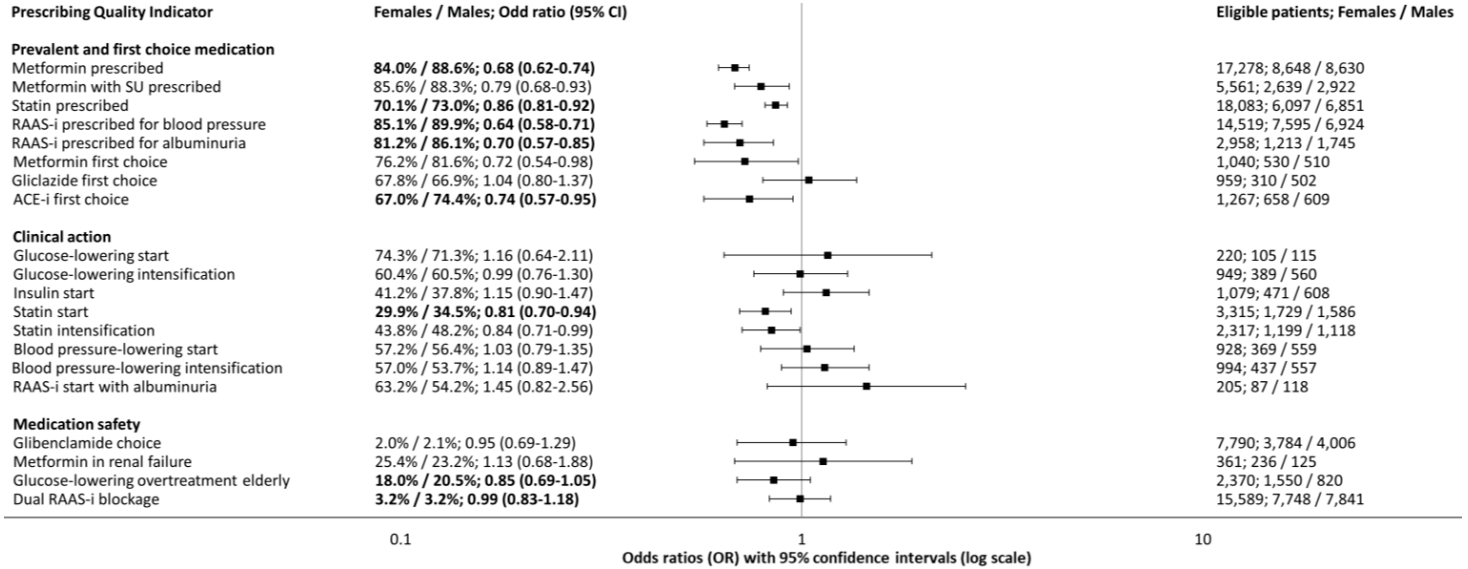
Supplemental Figure S1. Analyses of sex disparities in medication prescribing in 2019 adjusted for age, estimated glomerular filtration rate and cardiovascular disease. Odds ratios with 95% confidence intervals (log scale). The numbers of eligible patients are patients for whom the prescribing quality indicator could be calculated and applied.

Abbreviations: SU; sulfonylurea derivative, RAAS-i; renin-angiotensin aldosterone system, ACE-i; angiotensin-converting-enzyme inhibitor, OR; odds ratio, CI; confidence interval. *Note:* P<0.05 between females and males is marked bold. ORs below 1 indicate lower scores for females.

Supplementary table S1. Background characteristics and prescribed medication[a] for all included patients and by sex in the year 2012.

	Overall (N=26,093)	Males (n=12,861)	Females (n=13,232)	P-value
Age (years), mean ± SD	68 ± 12	66 ± 11	69 ± 12	<0.001
T2DM duration (years), median [IQR]	5.5 [2.4-9.5]	5.3 [2.3-9.0]	5.8 [2.6-10.0]	<0.001
BMI (kg/m²), mean ± SD	30.1 ± 5.4	29.5 ± 4.8	30.6 ± 6.0	<0.001
missing	3,240 (12)	1,547 (12)	1,693 (13)	
SBP >140 mmHg, n (%)	9,840 (38)	4,737 (37)	5,103 (39)	0.141
missing	3,306 (13)	1,764 (14)	1,542 (12)	
HbA1c >53 mmol/mol (7.0 %), n (%)	9,348 (36)	4,590 (36)	4,758 (36)	0.793
missing	2,493 (10)	1,298 (10)	1,195 (9)	
LDL-c >2.5 mmol/L, n (%)	9,585 (37)	4,258 (33)	5,327 (40)	<0.001
missing	5,021 (19)	2,467 (19)	2.554 (19)	
Albuminuria[b], n (%)	3,340 (13)	1,980 (15)	1,360 (10)	<0.001
missing	13,813 (53)	6,276 (49)	7,537 (57)	
eGFR (ml/min/1.73m²), mean ± SD	76 ± 20	79 ± 19	74 ± 20	<0.001
missing	3,898 (15)	1,065 (16)	1,833 (14)	
CVD, n (%)	8,022 (31)	4,310 (34)	3,712 (28)	<0.001
Glucose-lowering medication	20,062 (77)	10,088 (78)	9,974 (75)	<0.001
1	11,067	5,444	5,623	
2	7,701	3,958	3,743	
≥3	1,294	686	608	
Insulin	3,733 (14)	1,719 (13)	2,014 (15)	<0.001
Metformin	17,045 (65)	8,820 (69)	8,225 (62)	<0.001
SU-derivatives	7,790 (30)	4,006 (31)	3,784 (29)	<0.001
DPP-4 inhibitors	1,158 (4)	580 (5)	578 (4)	0.579
Blood pressure-lowering medication	19,938 (76)	9,628 (75)	10,310 (78)	<0.001
1	5,415	2,703	2,712	
2	6,602	3,178	3,424	
≥3	7,917	3,746	4,171	
RAAS inhibitors	15,589 (60)	7,841 (61)	7,748 (59)	<0.001
Calcium channel blockers	6,104 (23)	3,088 (24)	2,016 (23)	0.020
Beta blockers	10,659 (41)	5,100 (40)	5,559 (42)	<0.001
Diuretics	11,956 (46)	5,216 (41)	6,740 (51)	<0.001
Statins	17,506 (67)	9,065 (70)	8,441 (64)	<0.001

Abbreviations: T2DM = type 2 diabetes mellitus; BMI = body mass index; SBP = systolic blood pressure; HbA1c = glycosylated hemoglobin A1c; LDL-c = low density lipoprotein cholesterol; eGFR = estimated glomerular filtration rate; CVD = cardiovascular disease; SU = sulphonylurea; DPP-4 = dipeptidyl peptidase-4; RAAS = renin-angiotensin aldosterone system. *Note:* [a]Prescribed medication in the last 4 months of 2012. [b]Albuminuria was defined as albumin creatinine ratio ≥2.5 mg/mmol for males and ≥3.5 for females or albumin in 24h urine≥30 mg. P-values were obtained via independent t-tests (age and BMI), Mann-Whitney U test (T2DM duration), and Chi Square tests (SBP, HbA1c, LDL-c, albuminuria, and all prescribed medication).



Supplemental Figure S2. Unadjusted analyses of sex disparities in medication prescribing in 2012. Odds ratios with 95% confidence intervals (log scale). The numbers of eligible patients are patients for whom the prescribing quality indicator could be calculated and applied.

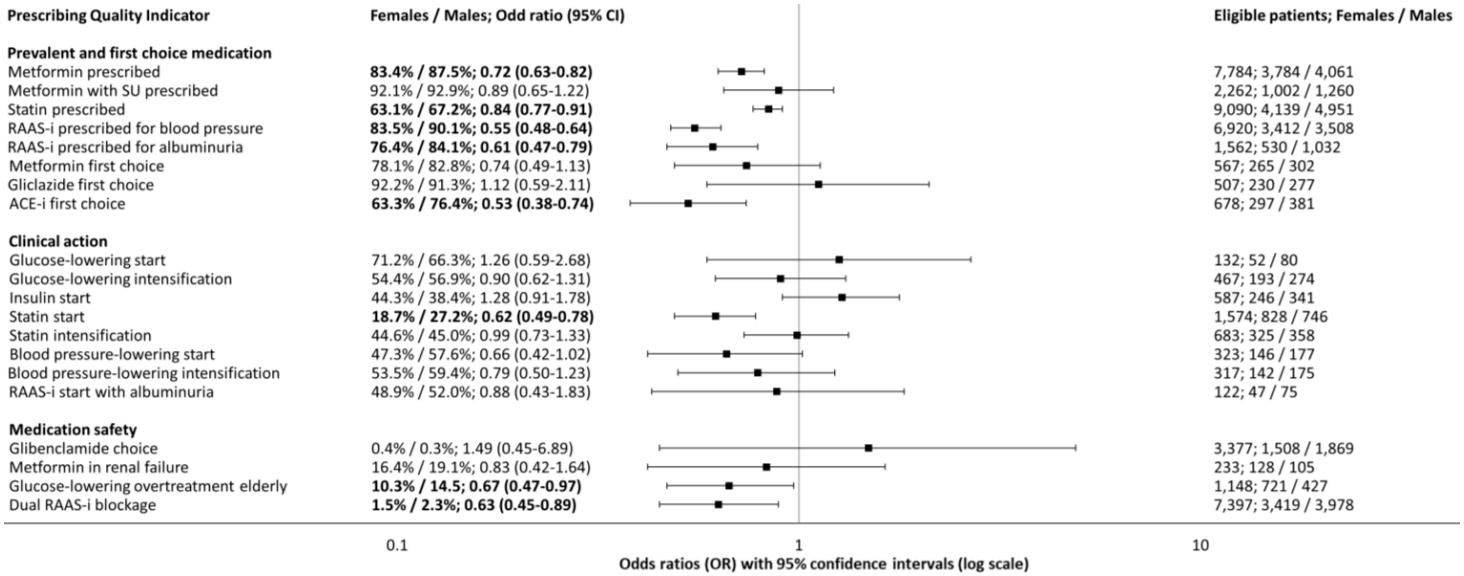
Abbreviations: SU; sulfonylurea derivative, RAAS-i; renin-angiotensin aldosterone system, ACE-i; angiotensin-converting-enzyme inhibitor, OR; odds ratio, CI; confidence interval.

Note: P<0.05 between females and males is marked bold. ORs below 1 indicate lower scores for females.

Supplementary table S2. Background characteristics and prescribed medication[a] for all included patients and by sex in the year 2017.

	Overall (N=13,271)	Males (n=6,836)	Females (n=6,435)	P-value
Age (years), mean ± SD	68 ± 12	67 ± 12	70 ± 13	<0.001
T2DM duration (years), median [IQR]	8.2 [4.8-13.0]	8.0 [4.6-12.6]	8.4 [4.9-13.3]	<0.001
BMI (kg/m²), mean ± SD	30.1 ± 5.6	29.5 ± 4.9	30.8 ± 6.1	<0.001
missing	1,716 (13)	907 (13)	809 (13)	
SBP >140 mmHg, n (%)	3,983 (30)	1,971 (29)	2,012 (31)	0.015
missing	2,394 (18)	1,286 (19)	1,108 (17)	
HbA1c >53 mmol/mol (7.0 %), n (%)	4,698 (35)	2,441 (36)	2,257 (35)	0.086
missing	2,362 (18)	1,271 (19)	1,091 (17)	
LDL-c >2.5 mmol/L, n (%)	4,412 (33)	2,037 (30)	2,375 (37)	<0.001
missing	3,465 (26)	1,797 (26)	1,668 (26)	
Albuminuria[b], n (%)	1,803 (14)	1,180 (17)	623 (10)	<0.001
missing	4,285 (32)	2,181 (32)	2,104 (33)	
eGFR (ml/min/1.73m²), mean ± SD	74 ± 21	75 ± 20	73 ± 21	<0.001
missing	2,620 (20)	1,438 (21)	1,182 (18)	
CVD, n (%)	4,810 (36)	2,625 (38)	2,185 (34)	<0.001
Glucose-lowering medication	9,477 (71)	5,014 (73)	4,463 (69)	<0.001
1	5,282	2,688	2,594	
2	3,517	1,933	1,584	
≥3	678	393	285	
Insulin	2,669 (20)	1,363 (20)	1,306 (20)	0.608
Metformin	7,774 (59)	4,206 (62)	3,568 (55)	<0.001
SU-derivatives	3,377 (25)	1,869 (27)	1,508 (23)	<0.001
DPP-4 inhibitors	505 (4)	282 (4)	223 (3)	0.047
GLP-1 analogues	298 (2)	132 (2)	166 (3)	0.012
SGLT2 inhibitors	86 (1)	49 (1)	37 (1)	0.309
Blood pressure-lowering medication	9,862 (72)	4,907 (72)	4,655 (72)	0.475
1	2,642	1,399	1,243	
2	3,195	1,579	1,616	
≥3	3,725	1,929	1,796	
RAAS inhibitors	7,397 (56)	3,978 (58)	3,419 (53)	<0.001
Calcium channel blockers	3,123 (24)	1,687 (25)	1,436 (22)	0.001
Beta blockers	5,082 (38)	2,563 (37)	2,519 (39)	0.050
Diuretics	5,513 (42)	2,583 (38)	2,930 (46)	<0.001
Statins	7,989 (60)	4,370 (64)	3,619 (56)	<0.001

Abbreviations: T2DM = type 2 diabetes mellitus; BMI = body mass index; SBP = systolic blood pressure; HbA1c = glycosylated hemoglobin A1c; LDL-c = low density lipoprotein cholesterol; eGFR = estimated glomerular filtration rate; CVD = cardiovascular disease; SU = sulphonylurea; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT2 = sodium-glucose cotransporter-2; RAAS = renin-angiotensin aldosterone system. *Note:* [a]Prescribed medication in the last 4 months of 2017. [b]Albuminuria was defined as albumin creatinine ratio ≥2.5 mg/mmol for males and ≥3.5 for females or albumin in 24h urine≥30 mg. P-values were obtained via independent t-tests (age and BMI), Mann-Whitney U test (T2DM duration), and Chi Square tests (SBP, HbA1c, LDL-c, albuminuria, and all prescribed medication).



Supplemental Figure S3. Unadjusted analyses of sex disparities in medication prescribing in 2017. Odds ratios with 95% confidence intervals (log scale). The numbers of eligible patients are patients for whom the prescribing quality indicator could be calculated and applied.

Abbreviations: SU; sulfonylurea derivative, RAAS-i; renin-angiotensin aldosterone system, ACE-i; angiotensin-converting-enzyme inhibitor, OR; odds ratio, CI; confidence interval.

Note: P<0.05 between females and males is marked bold. ORs below 1 indicate lower scores for females.

Supplementary table S3. Univariate subgroup analyses of sex disparities in medication prescribing in 2019. Odds ratios with 95% confidence intervals. *Abbreviations:* CVD; cardiovascular disease, SU; sulfonylurea, RAAS-i; renin-angiotensin aldosterone system inhibitor, ACE-i; angiotensin-converting-enzyme inhibitor, OR; odds ratio, CI; confidence interval. *Note:* P<0.05 between females and males is marked bold.

preferably landscape orientation	OR (95% CI)			
	Age		History of CVD	
Prevalent and first choice medication	< 60 years	≥60 years	yes	no
Metformin prescribed	**0.62 (0.44-0.89)**	**0.72 (0.62-0.83)**	**0.64 (0.53-0.76)**	**0.78 (0.62-0.98)**
Metformin with SU prescribed	0.44 (0.18-1.06)	0.85 (0.59-1.23)	0.79 (0.51-1.23)	0.71 (0.41-1.21)
Statin prescribed	**0.75 (0.57-0.97)**	**0.81 (0.73-0.90)**	**0.88 (0.79-0.99)**	**0.68 (0.57-0.81)**
RAAS-i prescribed for blood pressure	**0.49 (0.31-0.79)**	**0.56 (0.47-0.66)**	**0.53 (0.43-0.66)**	**0.56 (0.44-0.72)**
RAAS-i prescribed for albuminuria	0.52 (0.19-1.44)	**0.66 (0.49-0.88)**	0.72 (0.49-1.05)	**0.56 (0.37-0.85)**
Metformin first choice	0.41 (0.12-1.43)	0.77 (0.47-1.27)	**0.54 (0.30-0.98)**	0.96 (0.45-2.05)
Gliclazide first choice	0.39 (0.09-1.73)	0.95 (0.42-2.16)	0.55 (0.23-1.28)	1.75 (0.42-7.31)
ACE-i first choice	0.70 (0.28-1.73)	1.03 (0.68-1.56)	1.12 (0.71-1.78)	0.63 (0.33-1.22)
Clinical action				
Glucose-lowering start	1.74 (0.60-5.06)	0.37 (0.13-1.04)	0.78 (0.35-1.75)	0.44 (0.06-3.16)
Glucose-lowering intensification	1.13 (0.64-1.98)	0.84 (0.50-1.41)	0.89 (0.58-1.38)	1.25 (0.56-2.81)
Insulin start	0.91 (0.52-1.59)	0.72 (0.43-1.20)	0.74 (0.48-1.14)	1.06 (0.48-2.34)
Statin start	1.01 (0.64-1.62)	**0.66 (0.49-0.89)**	0.82 (0.62-1.09)	**0.50 (0.28-0.90)**
Statin intensification	1.45 (0.74-2.84)	1.12 (0.73-1.72)	1.44 (0.97-2.15)	0.52 (0.22-1.24)
Blood pressure-lowering start	1.35 (0.61-2.99)	0.91 (0.46-1.76)	0.91 (0.52-1.58)	3.10 (0.79-12.14)
Blood pressure-lowering intensification	**2.82 (1.03-7.71)**	0.85 (0.45-1.61)	1.12 (0.62-2.03)	1.42 (0.47-4.34)
RAAS-i start with albuminuria	2.06 (0.57-7.47)	1.17 (0.45-3.02)	1.73 (0.70-4.27)	0.76 (0.18-3.23)
Medication safety				
Glibenclamide choice	N per group too small		0.31 (0.03-2.80)	omitted
Metformin in renal failure	N per group too small		0.72 (0.28-1.89)	1.61 (0.63-4.11)
Glucose lowering overtreatment elderly	N per group too small		0.83 (0.46-1.51)	0.71 (0.40-1.27)
Dual RAAS-i blockage	1.14 (0.36-3.61)	0.64 (0.39-1.05)	0.74 (0.41-1.34)	0.66 (0.32-1.37)

6

Sex differences in lipid profile across the life span in patients with type 2 diabetes: A primary care-based study

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J. Clin. Med. 2021, 10(8), 1775

ABSTRACT

We assessed sex differences across the life span in the lipid profile of type 2 diabetes (T2D) patients treated and not treated with statins. We used the Groningen Initiative to ANalyze Type 2 diabetes Treatment database, which includes T2D patients from the north of the Netherlands. Patients with a full lipid profile determined between 2010 and 2012 were included. We excluded patients treated with other lipid-lowering drugs than statins. Sex differences in low- and high-density lipoprotein cholesterol (LDL-c and HDL-c) and triglyceride (TG) levels across 11 age groups stratified by statin treatment were assessed using linear regression. We included 26,849 patients (51% women, 55% treated with statins). Without statins, women had significantly lower LDL-c levels than men before the age of 45 years, similar levels between 45 and 49 years, and higher levels thereafter. With statins, similar LDL-c levels were shown up to the age of 55, and higher levels in women thereafter. Women had significantly higher HDL-c levels than men, regardless of age or statin treatment. Men had significantly higher TG levels up to the age of 55 and 60, depending on whether they did not take or took statins, respectively, and similar levels thereafter. When managing cardiovascular risk in patients with T2D, attention is needed for the menopausal status of women and for TG levels in younger men.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality in the world (1), and a person's lipid profile is an important aspect of the cardiovascular risk. It has been shown that men have a higher risk of atherosclerotic CVD than women (2) and that men develop CVD on average seven to ten years earlier than women (3). Women are assumed to have more cardiometabolic reserves associated with female sex hormones, which gives them a biologic advantage when it comes to cardiovascular risk (4–6). At younger ages, women have a more favorable lipid profile, characterized by lower levels of low-density lipoprotein cholesterol (LDL-c) and higher levels of high-density lipoprotein cholesterol (HDL-c) than men (7). During the menopausal transition, women develop a more adverse lipid profile, characterized by an increase in LDL-c and a decrease in HDL-c (8–11).

In patients with type 2 diabetes (T2D), the risk of CVD is at least doubled in comparison to patients without diabetes (12,13). Although T2D is a risk factor for both men and women, the impact of T2D on cardiovascular risk is markedly higher in women. Recent meta-analyses showed that T2D poses a 44% greater excess risk for coronary heart disease and a 27% greater excess risk for stroke in women compared to men (14,15). Sex differences in the lipid profile are likely to play a role in this, since women with T2D have higher LDL-c and HDL-c levels and lower triglyceride (TG) levels than men with T2D (16). It is not clear, however, whether such differences are present across all age groups and if they are influenced by menopausal status. This is likely, since a more atherogenic lipid and pro-inflammatory profile has been shown in postmenopausal diabetic women when compared to premenopausal non-diabetic or diabetic women (17).

To reduce cardiovascular risk in patients with T2D, a lipid-lowering treatment with a statin has been recommended for most of these patients, without differentiating between men and women (18,19). The Cholesterol Treatment Trialists' Collaborators have shown that the proportional reduction in major vascular events per mmol/L of LDL-c reduction with statins is similar between men and women with T2D (20). Since T2D increases the risk of CVD in women more than in men, women should be treated at least as stringently as men (6). Nonetheless, it seems that women with T2D are treated less aggressively with statins (21–23) and achieve cholesterol treatment targets less often than men (16,21,22,24–27).

Taken together, the above highlighted findings suggest that not only the presence of T2D but also menopausal status is relevant for the observed sex differences in cardiovascular risk. So far, a comprehensive analysis of sex differences in the lipid profile across the life span in patients with T2D is lacking. Furthermore, it is not clear to what extent possible sex differences across age groups can be mitigated by treat-

ment with statins. Therefore, the aim of this study was to assess differences in the lipid profile between men and women with T2D across the life span and to assess to what extent are such differences influenced by treatment with statins. This information can provide insight into potentially undertreated populations and help guide personalized treatment.

MATERIALS AND METHODS

Study design and population

We conducted a cross-sectional cohort study using data from the Groningen Initiative to ANalyse Type-2 diabetes Treatment (see GIANTT at https://umcgresearch.org/facilities, accessed on 7th of April 2021) database. This database contains anonymous primary care electronic medical record data from patients with T2D in the northern part of the Netherlands, including outcomes of diagnostic measurements and medication prescriptions. This population mostly consists of Caucasian people. The GIANTT data have been used for numerous studies (e.g. 23,28,29), including a study in which GIANTT was the reference care-as-usual cohort (30). Data imports are checked for completeness, and measurement units, coding of medication, and diagnostic measurements are harmonized before being imported in GIANTT.

Patients were included if they were treated by a general practitioner, had at least one full lipid profile (i.e., total cholesterol (TC), LDL-c, HDL-c, and TG) measurement between 1 January 2010 and 31 December 2012, had information about medical history of at least 180 days before the date of the lipid profile measurement, and were aged 18 years or older. We excluded patients without a known date of T2D diagnosis and those treated with other lipid-lowering drugs than statins (i.e., fibrates, bile acid sequestrants, nicotinic acid and derivatives, other lipid-modifying agents, or statins in a combination with other lipid-lowering drugs). The first date of the full lipid profile measurement was defined as the index date.

We obtained an exemption letter from the University Medical Center Groningen Medical Ethics Review Board (reference number M20.257509) indicating that an approval from the ethics committee was not needed for this study using anonymous data in the Netherlands.

Outcome variables

Our primary outcomes were the LDL-c, HDL-c, and TG levels in mmol/L at the index date. The secondary outcomes were the levels of TC and non-HDL cholesterol (non-HDL-c) at the index date.

Total cholesterol, LDL-c, HDL-c, and TG levels were assessed directly with standard enzymatic colorimetric methods (Roche elecsys C Module; Roche diagnostics, Switzerland) after an overnight fast. Non-HDL-c was calculated by subtracting HDL-c from TC.

Explanatory variables

Sex and age were included as explanatory variables in our analyses. Sex was used as registered in GIANTT and defined as man or woman. Age was calculated on the index date and categorized in 11 age groups: < 40 years, 40–44 years, 45–49 years,50–54 years, 55–59 years, 60–64 years, 65–69 years, 70–74 years, 75–79 years, 80–84 years, and ≥ 85 years.

Confounders

We considered including body mass index (BMI), glycated hemoglobin A1c (HbA1c), and smoking status (smoker vs. non-smoker) as possible confounders. BMI and HbA1c had less than 20% of missing values, which were imputed using multiple imputation by chained equations (MICE; Table S1). Smoking status was missing for more than 60% of patients and was therefore not included in our analyses.

Analyses

Patient characteristics per treatment group, sex, and age group were analyzed descriptively. More information about the time periods and definitions used for the patient characteristics can be found in Table S1.

We conducted linear regression analyses to assess differences in lipid levels between men and women across different age groups, including an interaction term between sex and age groups. BMI (continuous) was included as a possible confounder for all outcomes, since BMI differed between sex and age groups and it has been associated with the lipid profile. HbA1c (continuous) was included as a possible confounder in the analysis of TG due to its relationship with TG levels (31). Adjusted mean lipid levels with their 95% confidence intervals were estimated for all sex and age groups. The analyses were conducted separately for patients treated and not treated with a statin. Statin treatment was defined as the prescription of a statin in at least two out of three months before the index date. All statins prescribed and available in the study period were included, i.e., simvastatin, pravastatin, fluvastatin, atorvastatin, and rosuvastatin.

Sensitivity analyses were conducted for the primary outcome among those treated with a statin in which we additionally adjusted for moderate-intensity treatment (i.e., simvastatin, pravastatin, fluvastatin, atorvastatin < 40 mg, and rosuvastatin < 20 mg)

versus high-intensity treatment (i.e., atorvastatin ≥ 40 mg and rosuvastatin ≥ 20 mg) (18) with a statin (binary variable).

All analyses were conducted in Stata version 14 (Stata Corp., College Station, TX, USA), and two-sided p-values < 0.05 were considered statistically significant.

RESULTS

There were 26,849 patients included in this study (Figure 1), of which 13,733 (51%) were women, and 14,894 (55%) were treated with a statin. The proportion of patients treated with statins was higher among men than among women (58% vs. 53%). Among both non-treated and treated patients, women were older, had a longer diabetes duration, higher BMI, more often had an estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 m2, were more often treated with ≥5 chronic medications, and were less often smokers than men (Table 1). Treatment with any glucose-lowering medication was similar for men and women. A similar proportion of men and women not treated with statins had a history of CVD, whereas for those treated with statins, men were more likely than women to have a history of CVD. Men were also more often treated with a high-intensity statin than women. In the highest age groups, women appeared to have a longer diabetes duration (Table S2). In both sexes, BMI was lower with higher age, whereas blood pressure, eGFR, and albuminuria were more unfavorable with higher age. Polypharmacy was most common in elderly women (Table S2). The percentage of patients with statin treatment was highest in the age groups between 55 and 79 years, and lowest in, particularly, the younger as well as the oldest women (Table S2).

Low-Density Lipoprotein Cholesterol, High-Density Lipoprotein Cholesterol, and Triglycerides

In patients not treated with a statin, the mean BMI-adjusted LDL-c levels were above 3 mmol/L in all age groups except in men aged ≥85 years (Figure 2A, left panel). Women had significantly lower LDL-c levels than men up to the age of 45 years and significantly higher LDL-c levels after the age of 50 years (Figure 2A left panel; Table S3A).

In patients treated with a statin, the mean BMI-adjusted LDL-c levels were below 2.5 mmol/L in all age groups (Figure 2A, right panel). There were no significant differences in LDL-c levels between men and women up to the age of 55 years. Between the age 55 and 84 years, we observed significantly higher LDL-c levels in women than in men (Figure 2A right panel; Table S3B).

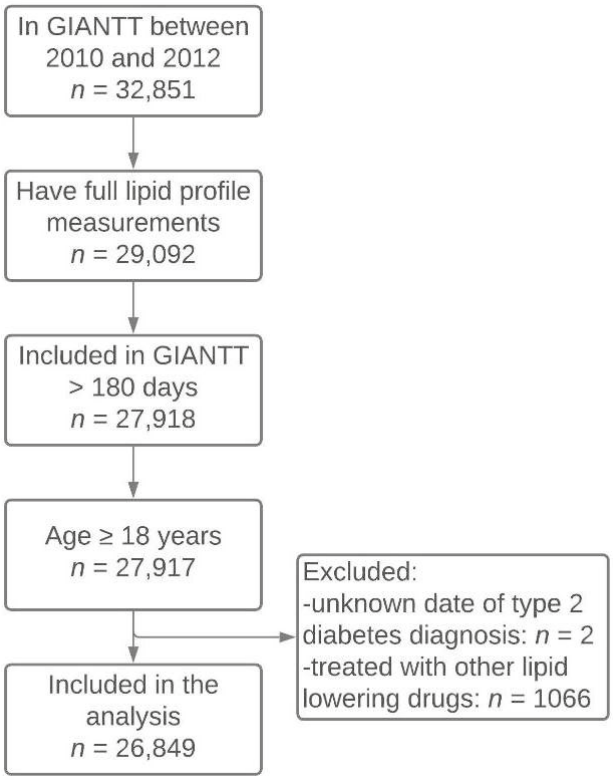


Figure 1. Flow chart with applied inclusion and exclusion criteria

Table 1: Demographics of included patients

	Not Treated with a Statin		Treated with a Statin	
	Men	**Women**	**Men**	**Women**
Number (%)	5549 (21)	6406 (24)	7567 (28)	7327 (27)
Age in years; mean ± SD	64 ± 12	68 ± 14	65 ± 11	68 ± 11
Diabetes duration; median (Q1–Q3)	2.5 (0.3–6.3)	3.0 (0.5–7.5)	4.6 (1.6–8.3)	5.2 (1.9–9.5)
HbA1c in % (mmol/mol); median (Q1–Q3) †	6.7 (50) (6.3–7.5)	6.7 (50) (6.3–7.3)	6.8 (51) (6.4–7.4)	6.8 (51) (6.4–7.3)
BMI in kg/m^2; mean ± SD †	29.4 ± 4.9	30.8 ± 6.1	29.8 ± 4.8	30.9 ± 5.8
SBP in mmHg; mean ± SD †	142 ± 19	143 ± 19	141 ± 18	142 ± 19
eGFR ≤ 60 mL/min/1.73 m^2; *n* (%) †	487 (10)	1049 (18)	802 (12)	1232 (18)
Albuminuria; *n* (%) †	82 (4)	64 (3)	146 (4)	118 (4)
Polypharmacy; *n* (%)	1361 (25)	2335 (36)	4420 (58)	4780 (65)
Glucose-lowering treatment; *n* (%)	3145 (57)	3631 (57)	5965 (79)	5769 (79)
Smoking; *n* (%) †	505 (25)	461 (20)	837 (27)	630 (21)
History of CVD, *n* (%) *	1014 (18)	1143 (18)	2681 (35)	2007 (27)

Table 1: Demographics of included patients (ontinued)

	Not Treated with a Statin		Treated with a Statin	
	Men	**Women**	**Men**	**Women**
LDL-c in mmol/L; mean ± SD	3.2 ± 0.9	3.4 ± 1.0	2.2 ± 0.7	2.3 ± 0.8
HDL-c in mmol/L; mean ± SD	1.2 ± 0.3	1.4 ± 0.4	1.2 ± 0.3	1.4 ± 0.4
Triglycerides in mmol/L; mean ± SD	1.9 ± 1.4	1.8 ± 1.0	1.8 ± 1.2	1.7 ± 0.9
TC in mmol/L; mean ± SD	5.1 ± 1.1	5.4 ± 1.1	4.0 ± 0.9	4.3 ± 0.9
Non-HDL-c in mmol/L; mean ± SD	3.9 ± 1.1	4.0 ± 1.1	2.9 ± 0.9	3.0 ± 0.9
Total/HDL-c ratio; mean ± SD	4.6 ± 1.5	4.2 ± 1.4	3.7 ± 1.1	3.3 ± 1.0
High intensity statin; *n* (%) ‡	n/a	n/a	693 (9)	499 (7)

† Glycated hemoglobin A1c (HbA1c): 627 (2.3%) missing values; Body mass index (BMI): 4403 (16.4%) missing values; Systolic blood pressure (SBP): 9852 (36.7%) missing values; Estimated glomerular filtration rate (eGFR): 2480 (9.2%) missing values; Albuminuria: 15,473 (57.6%) missing values; Smoking: 16,447 (61.3%) missing values. DDP-4: dipepti-dylpeptidase-4; CVD: cardiovascular disease; LDL: low-density lipoprotein; HDL: high-density lipoprotein; TC: total cholesterol. ˟ Includes any record of the presence of angina pectoris, acute myocardial infarction, transient ischemic attack, stroke, atherosclerosis, other ischemic heart diseases and peripheral arterial diseases, abdominal aortic aneurysm, per-cutaneous transluminal (coronary) angioplasty, and peripheral or coronary bypass before the index date. ‡ Daily dose of atorvastatin ≥ 40mg and rosuvastatin ≥ 20 mg; data on dose missing for eight patients.

Women had significantly higher BMI-adjusted HDL-c levels than men across all age groups, independent of statin treatment (Figure 2B, Table S3).

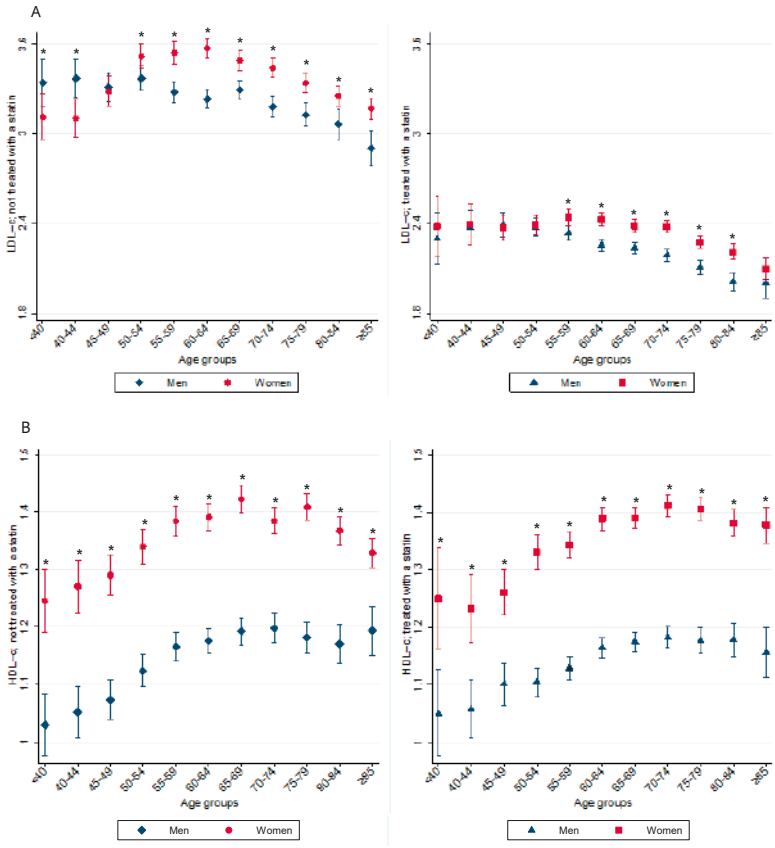
Men had significantly higher BMI- and HbA1c-adjusted TG levels than women up to the age of 55 and 60 years when not treated and treated with a statin, respectively, and similar levels thereafter (Figure 2C, Table S3).

The sensitivity analyses in which we additionally adjusted for the statin intensity showed similar results for LDL-c (Figure S1A), HDL-c (Figure S1B), and TGs (Figure S1C).

Total Cholesterol and Non-High-Density Lipoprotein Cholesterol

In patients not treated with a statin, TC and non-HDL-c levels showed similar sex and age patterns as seen for the LDL-c levels, with lower levels in women than in men younger than 45 and 50 years, respectively, and higher levels in women than in men after the age of 50 and 55 years, respectively (Figure S2A and B, Table S3).

For those treated with a statin, women and men had similar TC levels up to the age of 50 years, but women had higher levels than men thereafter (Figure S2A, Table S3). Non-HDL levels were higher in men than in women aged 45–49 years and higher in women than in men older than 60 years, but they were similar in both sexes in other age groups (Figure S2B, Table S3).



Age groups, N		<40	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	≥85
Not treated with a statin	Men	144	214	369	534	684	913	826	684	577	361	243
	Women	150	214	350	494	603	806	781	808	788	705	707
Treated with a statin	Men	70	157	308	628	934	1402	1359	1139	878	479	213
	Women	53	113	266	445	701	1068	1237	1146	1116	770	412

Figure 2. Mean lipid levels with 95% CIs for men and women per age group not treated (left) and treated with a statin (right). (A) Low-density lipoprotein cholesterol (LDL-c), (B) high-density lipoprotein cholesterol (HDL-c), and (C) triglyceride (TG) levels. Cholesterol measurements are in mmol/L. All values were adjusted for body mass index; TG values were additionally adjusted for glycated hemoglobin A1c. * $p < 0.05$ between men and women

DISCUSSION

This study showed that differences in lipid levels between women and men with T2D change substantially across the life span. For patients not treated with a statin, women had lower LDL-c levels than men before the age of 45 years and higher LDL-c levels after the age of 50 years. Statin treatment lowered LDL-c levels in both women and men, but women still had higher LDL-c levels than men after the age of 55 years. HDL-c levels were consistently higher in women than in men in all age groups, regardless of statin treatment. TG levels were higher in men than in women before the age of 60 years, regardless of statin treatment.

Comparison with Existing Literature

Sex differences in LDL-c levels in T2D have previously been reported, with women having higher levels than men (16,22,26). These studies did not allow for conclusions regarding age-dependent effects. Several other studies incorporated age in the analysis but divided the patients in only two age groups, using a cut-off of 60 or 65 years (21,24), or used broad age groups (32). In addition, these studies were limited by not stratifying the patients by statin use. Our study adds to this knowledge, showing that higher LDL-c levels in women than men occur only after the age of 50 and 55 years among T2D patients without or with statin treatment, respectively, which is around the mean age of menopause in the Netherlands (33). In line with our results, a previous study among 8775 T2D patients not stratifying for statin treatment found higher LDL-c levels in women than in men only after the age of 45 years (25). In contrast, a small study of 110 patients with T2D and 74 controls did not observe sex differences in LDL-c levels between diabetic pre- and postmenopausal women (17). This study, however, was limited by including only eight premenopausal diabetic women and did not stratify or adjust for statin treatment. Our findings show that unfavorable lipid profiles in women with T2D are particularly a postmenopausal phenomenon (10,11,34,35). Although sex differences in LDL-c levels have been acknowledged in the general population (2,7,11,36), this is the first study presenting a detailed analysis of the differences across age groups in a large cohort of patients with T2D. We observed similar differences with respect to non-HDL-c, a proposed atherogenic lipid risk marker for patients with T2D and non-diabetic individuals (37–39). The unfavorable lipid profile in women is not fully mitigated by statin treatment, since even with statin treatment, LDL-c and non-HDL-c levels in women remained higher than in men after the age of 55 years. This could be due to less intensive treatment in women (40,41), but the relationship between sex differences in treatment intensity and menopause has not been explored. We conducted a sensitivity analysis adjusting for statin intensity and observed a similar pattern of higher LDL-c levels among women after menopause.

Alternative explanations for these differences need further study by considering both possible sex- (biology and physiology) as well as gender- (behavior and psychology) related differences. To reach similar LDL-c levels, women with T2D above the age of 50 may have to be treated more aggressively than men. Although, on average, T2D patients treated with a statin achieved a level of LDL-c < 2.4 mmol/L, around half of the women between 55 and 75 years of age treated with statins showed higher LDL-c levels. Particularly, in patients with T2D and additional risk factors, lower LDL-c levels might be more appropriate (18,19,42). Our study illustrates that in women with T2D before menopause, there might still be a protective biological effect, which was previously assumed to be abrogated by the presence of T2D (17).

Previous studies looking at sex-related differences in HDL-c levels in patients with T2D reported higher HDL-c levels in women than in men (22,24,32), unrelated to patients' age (21,24). In line with these observations, we observed higher HDL-c levels in women in all age groups. Statin treatment did not affect HDL-c levels in our study, which is consistent with the mode of action of statins and previous research (42) and did not affect sex differences in HDL-c levels.

The high TG levels in younger and middle-aged men compared to women and older men have been observed previously in both the general population (7,43) and a population with T2D (25). Our findings add the observation that these high TG levels in younger men are not much lowered when patients are treated with statins. This observation could be explained by a higher BMI and more visceral fat in men (44,45) but, since our analyses were adjusted for BMI, this is an unlikely explanation. The higher TG levels in young men with T2D deserve further study, particularly since the combination of increased TG levels and low HDL-c levels has been associated with a 44% in-crease in the occurrence of major cardiovascular events also in patients with T2D (47).

Strengths and Limitations

A strength of our study is the use of realworld data from a large cohort of patients with T2D treated in primary care. To the best of our knowledge, it is the first study to investigate sex-related differences in lipid levels in these patients at different ages, with and without statin treatment. Our study also has some limitations. First, this is a cross-sectional design, so there can be potential historical demographic, nutritional, and healthcare system differences between older and younger patients included in our study. Also, mostly Caucasian people were included, which limits the application of the results to other races. Further, smoking could not be included as a confounder in the analyses due to the high proportion of missing data. Also, information on alcohol consumption and other lifestyle behaviors was not available in our database. Since such behaviors can differ between sexes and with age, this may have influenced

the results due to their effects on lipid levels. In addition, we could not adjust for potential differences between men and women regarding adherence to statins. Finally, there was no information about the start of menopause in the GIANTT database, but the mean age of menopause in the Netherlands has been estimated to be 50.4 ± 4.1 years (33).

Conclusions

Among younger patients with T2D, women seemed to have a more favorable lipid profile than men, since they had lower LDL-c and TG levels and higher HDL-c levels. Younger men with T2D had particularly high TG levels. Among patients with T2D older than 50 years, women had higher LDL-c levels than men. Statin treatment partly lowered the observed sex differences, but more than half of the patients with T2D were not treated with statins. When managing cardiovascular risk in patients with T2D, more attention is needed for the menopausal status of women and for TG levels in younger men.

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SUPPLEMENTARY MATERIAL

Table S1: Extraction time periods and definitions of variables used in the analyses.

Variable	Time period	Comment
Weight	Last value in five years before or first value in one year after index date	Height and weight were used to calculate BMI
Height	Last value in 10,000 days before or after index date	
BMI[1]	Last value in five years before or first value in one year after index date	BMI was extracted if height and/or weight were missing
HbA1c[1], smoking status, SBP	Last value in 6 months before index date or first value in 30 days after index date	Used as entered in the database
Serum creatinine* and eGFR	Last value in 6 months before index date or first value in 30 days after index date	eGFR was calculated using Modification of Diet in Renal Disease equation or extracted from the database[2] when serum creatinine was missing
Albumin creatinine ratio and albuminuria concentration	Last value in 6 months before index date or first value in 30 days after index date	Albuminuria was defined as albumin creatinine ratio ≥30 mg/g or albuminuria concentration ≥300 mg
Diabetes duration	On index date	
Polypharmacy and glucose lowering treatment	Based on prescriptions in the 3 months before index date	Polypharmacy was defined as a prescription for five or more drugs
History of CVD	Any recording of CVD before index date.	History of CVD included the presence of angina pectoris, acute myocardial infarction, transient ischemic attack, stroke, atherosclerosis, other ischemic heart diseases and peripheral arterial diseases, abdominal aortic aneurysm, percutaneous transluminal (coronary) angioplasty, and peripheral or coronary bypass.

*The standard way of measuring serum creatinine was directly with enzymatic colorimetric methods (Roche elecsys C Module; Roche diagnostics, Switzerland). [1] Multiple imputation by chained equation was used to impute BMI and HbA1c missing values. The model included LDL-c, HDL-c, TC, TG, and sex. No auxiliary variables were found. We conducted 20 imputations and the results of different datasets were combined by Stata using Rubin's combination rules. [2] eGFR in the database was calculated using the Modification of Diet in Renal Disease equation.

Table S2: Patient demographics in those not treated and treated with a statin per sex and age group.

			Number of patients	Diabetes duration; median	HbA1c; median	BMI in kg/m^2; mean	SBP in mmHg; mean	eGFR ≤60 mL/min/1.73m^2; N (%)	Albuminuria; N (%)	Polypharmacy; N (%)	Smoking; N (%)	History of CVD; N (%)
Not treated with a statin	Men	<40	144	1.0	7.1	32.1	133	0 (0)	2 (3)	7 (5)	29 (50)	2 (1)
		40-44	214	1.0	6.9	31.7	137	2 (1)	2 (2)	24 (11)	33 (42)	10 (5)
		45-49	369	0.9	6.8	31.1	138	1 (0)	3 (2)	47 (13)	40 (34)	21 (6)
		50-54	534	1.4	6.8	30.8	138	5 (1)	4 (2)	95 (18)	82 (38)	47 (9)
		55-59	684	2.0	6.7	29.7	140	12 (2)	8 (3)	121 (18)	67 (27)	77 (11)
		60-64	913	2.6	6.7	29.5	143	28 (3)	8 (2)	203 (22)	83 (25)	144 (16)
		65-69	826	2.9	6.7	29.6	145	50 (7)	10 (3)	187 (23)	59 (20)	155 (19)
		70-74	684	3.0	6.7	28.3	146	81 (13)	12 (4)	182 (27)	52 (21)	181 (26)
		75-79	577	3.9	6.7	28.4	147	109 (21)	14 (5)	226 (39)	31 (16)	159 (28)
		80-84	361	4.0	6.7	27.5	144	115 (35)	6 (4)	143 (40)	19 (14)	124 (34)
		≥85	243	5.6	6.8	26.3	145	84 (36)	13 (11)	126 (52)	10 (11)	94 (39)
	Women	<40	150	1.3	7.0	34.4	130	0 (0)	1 (1)	24 (16)	13 (25)	4 (3)
		40-44	214	1.2	6.6	33.3	132	4 (2)	1 (1)	35 (16)	15 (18)	10 (5)
		45-49	350	1.0	6.7	33.6	136	5 (2)	0 (0)	75 (21)	35 (26)	41 (12)
		50-54	494	1.4	6.8	32.7	139	17 (4)	2 (1)	129 (26)	75 (39)	46 (9)
		55-59	603	1.5	6.7	31.8	138	26 (5)	3 (2)	148 (25)	69 (28)	53 (9)
		60-64	806	2.2	6.7	31.0	142	51 (7)	3(1)	229 (28)	66 (20)	99 (12)
		65-69	781	2.9	6.7	30.8	146	82 (12)	6 (2)	240 (31)	54 (19)	128 (16)
		70-74	808	3.1	6.7	30.2	146	121 (17)	5 (2)	335 (41)	54 (19)	167 (21)
		75-79	788	4.0	6.7	29.8	146	176 (24)	14 (5)	351 (45)	41 (14)	192 (24)
		80-84	705	4.8	6.7	29.0	146	250 (38)	10 (4)	363 (51)	18 (8)	203 (29)
		≥85	707	7.4	6.8	28.1	145	317 (47)	19 (7)	406 (67)	21 (9)	200 (28)

Table S2: Patient demographics in those not treated and treated with a statin per sex and age group. (continued)

			Number of patients	a statin out of all in age group (%)	Diabetes duration; median	HbA1c; median	BMI in kg/m^2; mean	SBP in mmHg; mean	eGFR ≤60 mL/ min/1.73m^2; N (%)	Albuminuria; N (%)	Polypharmacy; N (%)	Smoking; N (%)	History of CVD; N(%)
Treated with a statin	Men	<40	70	33	3.2	6.7	33.2	132	0 (0)	2 (5)	16 (23)	10 (29)	4 (6)
		40-44	157	42	2.9	6.9	31.8	134	2 (1)	0 (0)	59 (38)	32 (43)	17 (11)
		45-49	308	45	2.9	6.8	31.7	136	1 (0)	3 (2)	117 (38)	54 (47)	44 (14)
		50-54	628	54	3.7	6.8	30.8	138	13 (2)	6 (2)	295 (47)	99 (38)	122 (19)
		55-59	934	58	4.3	6.9	30.6	138	27 (3)	11 (2)	476 (51)	113 (33)	251 (27)
		60-64	1,402	61	4.5	6.8	30.1	140	56 (4)	27 (4)	770 (55)	183 (30)	425 (30)
		65-69	1,359	62	4.7	6.8	29.8	144	109 (9)	24 (3)	797 (59)	137 (25)	490 (36)
		70-74	1,139	62	4.8	6.8	28.9	142	156 (15)	24 (4)	733 (64)	106 (22)	503 (44)
		75-79	878	60	5.5	6.8	28.7	143	199 (24)	24 (5)	628 (72)	65 (19)	438 (50)
		80-84	479	57	5.9	6.8	28.1	143	159 (35)	15 (6)	360 (75)	29 (15)	261 (54)
		≥85	213	47	6.9	6.9	27.1	142	80 (40)	10 (10)	169 (79)	9 (10)	127 (60)
	Women	<40	53	26	2.7	6.7	35.9	129	0 (0)	0 (0)	21 (40)	9 (43)	5 (9)
		40-44	113	35	2.7	6.8	34.3	131	0 (0)	1 (2)	54 (48)	13 (25)	19 (17)
		45-49	266	43	3.5	6.8	34.5	134	6 (3)	1 (1)	133 (50)	35 (30)	40 (15)
		50-54	445	47	3.8	6.8	32.6	135	13 (3)	8 (4)	241 (54)	73 (39)	68 (15)
		55-59	701	54	4.2	6.8	31.7	138	40 (6)	9 (3)	389 (55)	78 (27)	134 (19)
		60-64	1,068	57	4.6	6.7	31.3	140	85 (9)	13 (3)	627 (59)	122 (27)	214 (20)
		65-69	1,237	61	5.1	6.8	30.9	143	143 (13)	11 (2)	782 (63)	107 (21)	321 (26)
		70-74	1,146	59	5.5	6.8	30.6	144	201 (19)	20 (4)	794 (69)	86 (19)	353 (31)
		75-79	1,116	59	6.0	6.8	29.8	145	311 (30)	23 (5)	800 (72)	63 (14)	363 (33)
		80-84	770	52	7.3	6.8	29.2	147	273 (38)	21 (6)	599 (78)	33 (12)	309 (40)
		≥85	412	37	9.2	6.9	28.1	147	161 (41)	11 (6)	340 (83)	11 (7)	183 (44)

Table S3: Sex differences in lipid levels across age groups adjusted for BMI in those (A) not treated and (B) treated with a statin. Cholesterol measurements are in mmol/L. p<0.05 was statistically significant (bold); SE = standard error; LDL-c = low-density lipoprotein cholesterol; HDL-c = high-density lipoprotein cholesterol; TG = triglycerides; TC = total cholesterol

A – Not treated		<40	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	≥85
LDL-c; mean±SE	Men	3.3±.08	3.4±.06	3.3±.05	3.4±.04	3.3±.04	3.2±.03	3.3±.03	3.2±.04	3.1±.04	3.1±.05	2.9±.06
	Women	3.1±.08	3.1±.06	3.3±.05	3.5±.04	3.5±.04	3.6±.03	3.5±.03	3.4±.03	3.3±.03	3.3±.04	3.2±.04
	p	**0.039**	**0.004**	0.701	**0.012**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.002**	**<0.001**
HDL-c; mean±SE	Men	1.0±.03	1.1±.02	1.1±.02	1.1±.01	1.2±.01	1.2±.01	1.2±.01	1.2±.01	1.2±.01	1.2±.02	1.2±.02
	Women	1.2±.03	1.3±.02	1.3±.02	1.3±.02	1.4±.01	1.4±.01	1.4±.01	1.4±.01	1.4±.01	1.4±.01	1.3±.01
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
TG; mean±SE	Men	2.4±.09	2.5±.08	2.5±.06	2.3±.05	2.0±.04	1.9±.04	1.8±.04	1.7±.04	1.8±.05	1.6±.06	1.6±.07
	Women	1.7±.09	1.7±.08	1.8±.06	1.9±.05	1.8±.05	1.8±.04	1.8±.04	1.8±.04	1.8±.04	1.8±.04	1.7±.04
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.068	0.564	0.645	0.056	0.687	0.073	0.475
TC; mean±SE	Men	5.3±.09	5.4±.07	5.3±.06	5.4±.05	5.2±.04	5.1±.04	5.1±.04	5.0±.04	5.0±.05	4.9±.06	4.7±.07
	Women	5.0±.09	5.0±.07	5.2±.06	5.5±.05	5.6±.04	5.6±.04	5.6±.04	5.5±.04	5.4±.04	5.3±.04	5.1±.04
	p	**0.030**	**0.001**	0.259	**0.008**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Non-HDL-c; mean±SE	Men	4.2±.09	4.3±.07	4.2±.06	4.2±.05	4.0±.04	3.9±.04	4.0±.04	3.8±.04	3.8±.05	3.7±.06	3.5±.07
	Women	3.8±.09	3.7±.07	3.9±.06	4.2±.05	4.2±.04	4.2±.04	4.1±.04	4.1±.04	4.0±.04	3.9±.04	3.8±.04
	p	**<0.001**	**<0.001**	**<0.001**	0.591	**<0.001**	**<0.001**	**0.001**	**<0.001**	**0.001**	**0.002**	**<0.001**
B – Treated												
LDL-c; mean±SE	Men	2.3±.09	2.4±.06	2.4±.04	2.4±.03	2.3±.02	2.3±.02	2.2±.02	2.2±.02	2.1±.02	2.0±.03	2.0±.05
	Women	2.4±.10	2.4±.07	2.4±.05	2.4±.03	2.4±.03	2.4±.02	2.4±.02	2.4±.02	2.3±.02	2.2±.03	2.1±.04
	p	0.534	0.820	0.767	0.747	**0.004**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.116
HDL-c; mean±SE	Men	1.1±.04	1.1±.03	1.1±.02	1.1±.01	1.1±.01	1.2±.01	1.2±.01	1.2±.01	1.2±.01	1.2±.01	1.2±.02
	Women	1.3±.04	1.2±.03	1.3±.02	1.3±.02	1.3±.01	1.4±.01	1.4±.01	1.4±.01	1.4±.01	1.4±.01	1.4±.02
	p	**0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**

TG; mean±SE	Men	2.2±.12	2.4±.08	2.2±.06	2.1±.04	1.9±.03	1.8±.03	1.7±.03	1.6±.03	1.6±.03	1.6±.05	1.5±.07
	Women	1.8±.14	1.7±.10	1.8±.06	1.8±.05	1.8±.04	1.8±.03	1.7±.03	1.7±.03	1.6±.03	1.6±.04	1.6±.05
	p	**0.028**	**<0.001**	**<0.001**	**<0.001**	**0.006**	0.867	0.158	0.089	0.143	0.491	0.254
TC; mean±SE	Men	4.1±.11	4.3±.07	4.3±.05	4.2±.04	4.2±.03	4.1±.02	4.0±.02	4.0±.03	3.9±.03	3.8±.04	3.7±.06
	Women	4.3±.12	4.2±.08	4.3±.05	4.4±.04	4.4±.03	4.5±.03	4.4±.03	4.4±.03	4.3±.03	4.2±.03	4.1±.04
	p	0.385	0.811	0.567	**0.024**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Non-HDL-c; mean±SE	Men	3.1±.10	3.2±.07	3.2±.05	3.1±.03	3.0±.03	2.9±.02	2.9±.02	2.8±.03	2.7±.03	2.6±.04	2.5±.06
	Women	3.0±.12	3.0±.08	3.0±.05	3.0±.04	3.1±.03	3.1±.03	3.0±.02	3.0±.03	2.9±.03	2.8±.03	2.7±.04
	p	0.707	0.063	**0.006**	0.059	0.141	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.044**

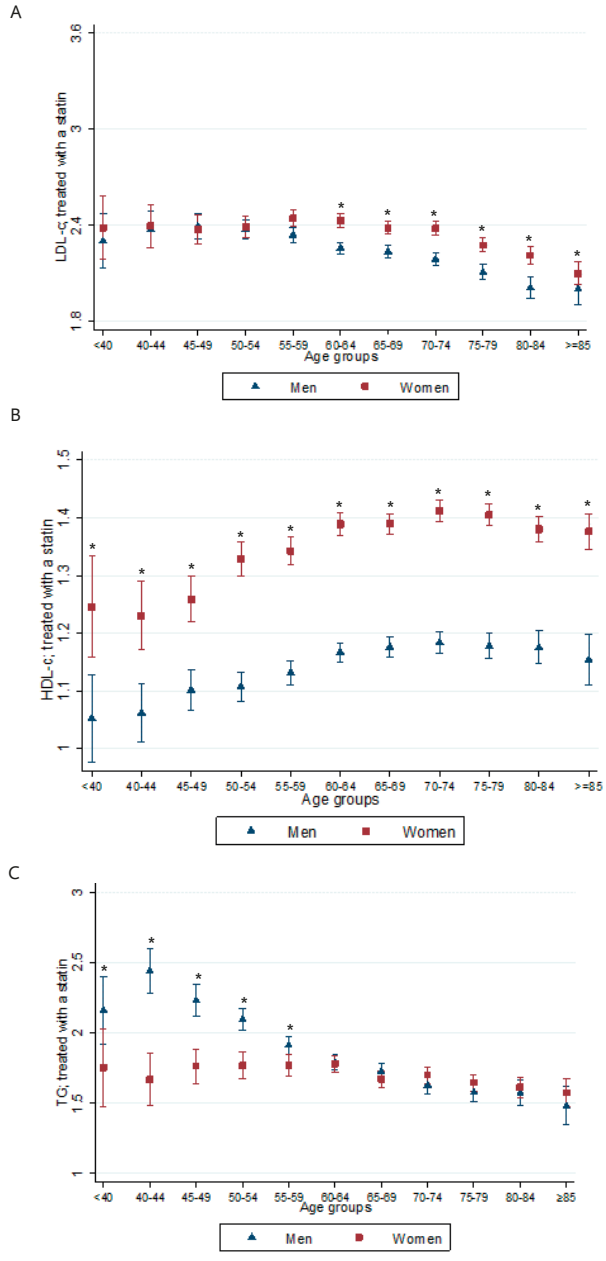

Figure S1: Mean lipid levels with 95% CIs for men and women per age group treated by a statin of (A) low-density lipoprotein cholesterol (LDL-c), (B) high-density lipoprotein cholesterol (HDL-c) and (C) triglycerides (TG). Cholesterol measurements are in mmol/L. Values are adjusted for body mass index and statin dose (moderate versus high; dose was not available for 8 patients); TG values are additionally adjusted for glycated hemoglobin A1c. *p<0.05 between men and women.

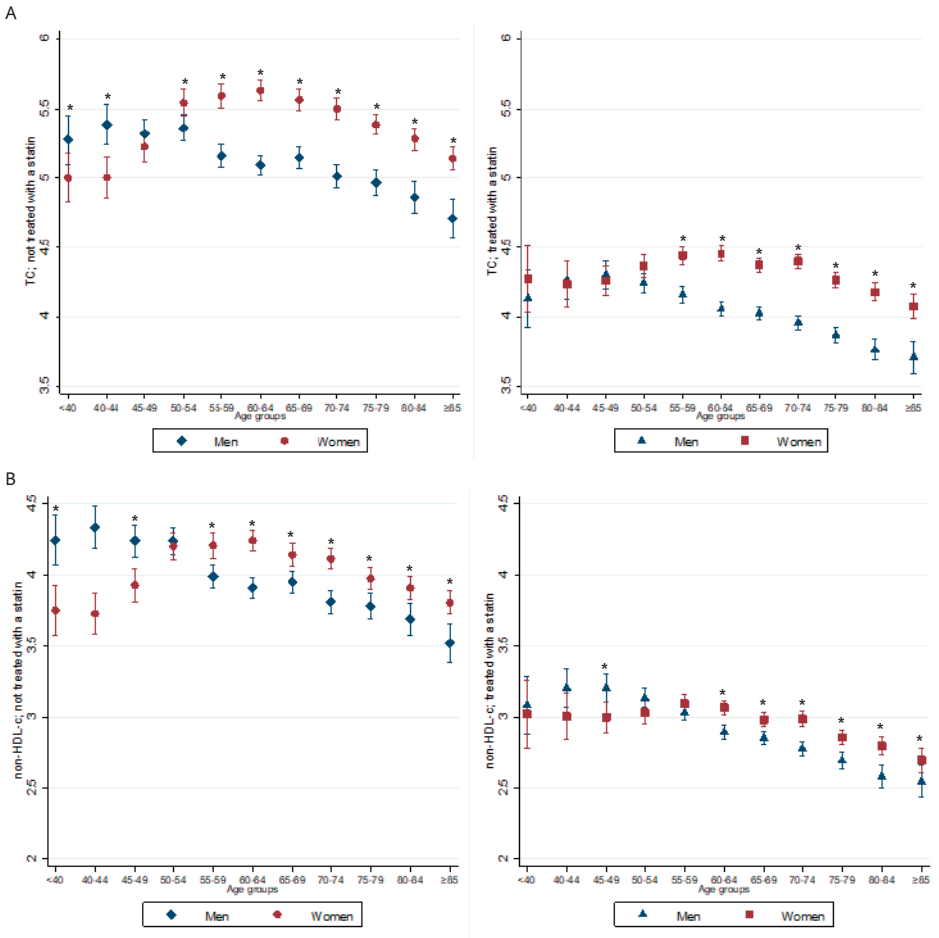

Figure S2: Mean lipid levels with 95% CIs for men and women per age group in those not treated (left) and treated with a statin (right) of (A) total cholesterol (TC) and (B) non-HDL cholesterol. Cholesterol measurements are in mmol/L. All values are adjusted for body mass index (BMI); TG values are additionally adjusted for glycated hemoglobin A1c. *p<0.05 between men and women.

7

Older age, polypharmacy, and low systolic blood pressure are associated with more hypotension-related adverse events in patients with type 2 diabetes treated with antihypertensives

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ABSTRACT

Background and Aims

Low systolic blood pressure (SBP) levels while being treated with antihypertensives may cause hypotension-related adverse events (hrAEs), especially in the elderly, women, and frail patients. We aimed to assess the association between the occurrence of hrAEs and low SBP levels, age, sex, and polypharmacy among patients with type 2 diabetes (T2D) treated with antihypertensives.

Methods

In this cohort study, we used the Groningen Initiative to ANalyse Type 2 diabetes Treatment (GIANTT) database which includes patients managed for T2D in primary care from the north of the Netherlands. Patients treated with ≥1 antihypertensive drug and ≥1 SBP measurement between 2012 and 2014 were included. The outcome was the presence of an hrAE, i.e. postural hypotension, dizziness, weakness/tiredness, and syncope in 90 days before or after the lowest recorded SBP level. Age (≥70 vs. <70 years), sex (women vs. men), polypharmacy (5 to 9 drugs or ≥10 drugs vs. <5 drugs), and SBP level (<130 or ≥130 mmHg) were included as determinants. Logistic regression analyses were conducted for age, sex and polypharmacy, including the SBP level and their interaction, adjusted for confounders. Odds ratios (OR) with 95% confidence intervals (CI) are presented.

Results

We included 21,119 patients, 49% of which were ≥70 years old, 52% were women, 57% had polypharmacy, 61% had an SBP level <130mmHg and 5.4% experienced an hrAE. Patients with an SBP level <130mmHg had a significantly higher occurrence of hrAEs than patients with a higher SBP level (6.2% vs. 4.0%; ORs 1.41, 95%CI 1.14-1.75; 1.43, 95%CI 1.17-1.76 and 1.33, 95%CI 1.06-1.67). Older patients (OR 1.29, 95%CI 1.02-1.64) and patients with polypharmacy (OR 5-9 drugs 1.27, 95%CI 1.00-1.62; OR ≥10 drugs 2.37, 95% CI 1.67-3.37) were more likely to experience an hrAE. The association with sex and the interactions between the determinants and SBP level were not significant.

Conclusions

Low SBP levels in patients with T2D treated with antihypertensives is associated with an increase in hrAEs. Older patients and those with polypharmacy are particularly at risk of hrAEs. Age, sex, and polypharmacy did not modify the risk of hrAEs associated with a low SBP level.

INTRODUCTION

Blood pressure targets for patients with type 2 diabetes (T2D) are commonly lower in comparison to the general population because of their increased risk of cardiovascular (CV) morbidity and mortality (1-3). Several guidelines and clinical trials suggest to lower SBP below 130 or even 120 mmHg in all patients with T2D, implying that the benefits outweigh possible risks of treatment (1, 4-8). However, there are concerns that treatment to low SBP levels increases the occurrence of adverse events (AEs) (9-11). A meta-analysis from 2016 which included almost 180,000 participants, several of which had T2D, observed that a reduction of SBP below 130 mmHg prevents one major CV event but is associated with six treatment discontinuations due to intercurrent conditions or serious AEs (12). Further, lower SBP levels have been associated with higher mortality in T2D patients older than 75 years vs. 60 to 75 years treated with antihypertensive drugs (13), which suggests that the optimal SBP target may differ across subpopulations. Also, the occurrence of treatment-related AEs seems to differ between patient groups since studies have shown a higher risk of drug-related AEs among women (14-17), older, and frail patients (17-20).

Several studies from clinical practice show that up to 20% of patients with T2D have SBP levels <130 mmHg while receiving multiple antihypertensive drugs or medication treatment intensification (21-23). This percentage is even higher in the elderly or frail, where more than half of the patients have SBP levels <130 mmHg (24, 25). These low SBP levels can lead to hypotension-related AEs, including syncope, tiredness, and postural hypotension (4, 26), and could indicate overtreatment with antihypertensives. Although one might expect that specific patient groups are more vulnerable for these AEs when they are treated to low blood pressure levels, no significant age-by-treatment interaction effect was seen in adults included in the SPRINT trial (18). However, participants with diabetes, history of stroke, heart failure, dementia or standing SBP less than 110 mmHg were excluded from this trial. Since T2D can affect the cardiovascular and renal system, patients with T2D may have a different risk of AEs from antihypertensive treatment than those without T2D (27). Whether the occurrence of hypotension-related AEs in T2D patients treated to low SBP levels is affected by age or other patient characteristics is unknown.

Our aim was to assess the association between the occurrence of hypotension-related AEs and low SBP levels, age, sex, and polypharmacy among patients with T2D treated with antihypertensives in general practice. Our first hypothesis was that patients with low SBP levels but also older patients, women, and those with polypharmacy more often experience a hypotension-related AE. Furthermore, we aimed to assess whether age, sex, and polypharmacy influence the association between low SBP levels and hypotension-related AEs. We hypothesized that the risk of hypotension-

related AEs when having low SBP levels is intensified in older patients, females, and those with polypharmacy. Insight in possible differences in such risks among patient groups is important to guide more personalized treatment of hypertension in patients with T2D.

MATERIALS AND METHODS

Study design and population

In this cross-sectional cohort study, we used the Groningen Initiative to ANalyse Type-2 diabetes Treatment (GIANTT; www.giantt.nl) database. This database contains anonymous electronic medical records data of patients managed for T2D in primary care from the northern part of the Netherlands.

We included patients with at least one SBP measurement between the years 2012 to 2014. The day of the lowest SBP measurement in this time period was defined as index date. In case the lowest SBP level was recorded multiple times, the date of the first measurement was used. Patients had to have a practitioner confirmed diagnosis of T2D before the index date, had to be 18 years or older at the index date, and had to have at least 90 days of medical history before and 90 days of follow-up after index date to be included in our study. Patients without a prescription of an antihypertensive drug (anatomic therapeutic chemical (ATC) classification codes C02, C03, C07, C08, C09) in 90 days before the index date were excluded. Data were available from 189 general practices in the study period, after excluding data from three practices that had not documented any hypotension-related diagnostic codes in the study period.

We obtained an exemption letter for full ethical approval from the University Medical Center Groningen Medical Ethics Review Board (reference number M20.252895), since we used anonymous medical record data for this study.

Outcome variable

Our primary outcome was the presence of a hypotension-related AE in the 90 days before or after index date. This time window was chosen because an AE may be documented after the measurement of a low SBP, or the blood pressure may have been measured after the occurrence of an AE. The AEs were chosen based on the literature (4, 26), and defined with International Classification of Primary Care (ICPC) diagnostic codes used in Dutch primary care. The following diagnostic codes were included as hypotension-related AEs: K88 (postural hypotension), N17 (dizziness, vertigo), A04 (weakness, tiredness, lethargy), and A06 (syncope).

Determinants

Age (≥70 vs. <70 years), sex (women vs. men), polypharmacy (polypharmacy (5 to 10 drugs) or hyper polypharmacy (≥10 drugs) vs. no polypharmacy) and SBP level (<130 mmHg vs. ≥130 mmHg) were included as determinants that may influence the occurrence of hypotension-related AEs. Age, sex and SBP level measured in the practice as documented at index date were used. Polypharmacy was based on the number of medications at the 3rd pharmacological subgroup level of the ATC classification that a patient was prescribed in a period of 90 days up to the index date in addition to the one antihypertensive drug all patients had been prescribed by design.

Confounders

The following patient characteristics available from the medical record data in GIANTT that may be associated with the selected AEs and with the SBP level and/or can differ between patients with different age, sex and polypharmacy, were included as potential confounders: glycated hemoglobin (HbA1c) level (continuous variable), duration of diabetes (<10 years or ≥10 years), smoking status (smoker or non-smoker), diastolic blood pressure level (continuous variable), body mass index (BMI; continuous variable), presence of decreased estimated glomerular filtration rate (eGFR; <60 mL/min; calculated using the serum creatinine from GIANTT and Chronic Kidney Disease Epidemiology Collaboration formula or extracted from the database if creatinine levels were missing), presence of albuminuria (albumin creatinine ratio ≥30 mg/g or albumin in 24h urine ≥300 mg), presence of dyslipidemia (defined as low density lipoproteins (LDL) ≥2.5 mmol/L), prescribed lipid lowering medication (none, 1 drug, ≥2 drugs) and glucose lowering medication (none, 1 oral drug, ≥2 oral drugs and/or insulin). Laboratory values were extracted as the last value in 180 days up to the index date or, in case that was not available, the first value in 90 days after index date. Diabetes duration was calculated on index date. Smoking status was assessed in the 180 days up to index date. BMI was calculated based on patients' weight closest to the index date in the five years before or one year thereafter and the most recent height recorded any time before or after index date. If height and/or weight were not available, the BMI as entered in GIANTT was used. Presence of prescriptions was calculated in the 90 days up to index date.

Missing data

There were no missing values for the determinants and the primary outcome. Confounders with less than 30% of missing values were imputed using multiple imputation by chained equation (MICE) (28). Patients with a missing value for albuminuria (59%) were classified as not having albuminuria, since such testing was less likely in

patients without expected kidney damage. None of the other confounders had more than 30% missing values.

Analyses

Demographics were analyzed descriptively for patients with and without hypotension-related AEs. For each of the determinants, a logistic regression analysis was conducted including the SBP level and the interaction between SBP level and age, sex, and polypharmacy. These analyses were adjusted for the potential confounders to assess the odds ratios (ORs) for the occurrence of hypotension-related AEs. In the analysis of polypharmacy, there was no adjustment for glucose and lipid lowering therapy since these variables are part of the calculation of polypharmacy. In the analyses where age, sex, or polypharmacy were not used as a determinant, they were included as continuous (age and polypharmacy) or dichotomous (sex) confounding variables.

Several sensitivity analyses were conducted. First, we conducted a sensitivity analysis using a higher cut-off level for age of 80 years and using both higher and lower cut-off levels for SBP of 140 and 120 mmHg, respectively. Next, we expanded the definition of the outcome to include other less specific ICPC diagnostic codes that may be related to hypotension: A80 (trauma, injury), L75 (femur fracture), L76 (other fracture), L81 (musculoskeletal injury), S16 (bruise, concussion) and S17 (abrasion, scratch).

All analyses were conducted in Stata version 14 (Stata Corp., College Station, TX). P-values <0.05 were considered statistically significant and ORs with 95% confidence intervals (CIs) are presented.

RESULTS

We included 21,119 patients with T2D treated with antihypertensives who met our inclusion criteria (Figure S1), of which 1,135 (5.4%) experienced a hypotension-related AE (Table 1). Forty nine percent of the included patients were older than 70 years, 52% were women, 57% had polypharmacy or hyper polypharmacy and 61% had the lowest SBP level below 130 mmHg. Patients who experienced a hypotension-related AE were more often women, older, had a longer diabetes duration and had more often eGFR ≤ mL/min/1.73m2 (Table 1). Almost half of the patients with a recorded AE had postural hypotension. Complete data were available for 52% of the patients.

Table 1: Patient characteristics

		No adverse event (N = 19,984)	Adverse event (N = 1,135)
Female; N (%)		10,275 (51)	632 (56)
Lowest SBP in mmHg; mean ± SD		125 ± 14	121 ± 16
Lowest SBP < 130 mmHg, N (%)		12,079 (60)	802 (71)
Age; mean ± SD		69 ± 11	71 ± 12
Age ≥ 70 years; N (%)		9,753 (49)	685 (60)
Polypharmacy; N (%)	no	8,818 (44)	351 (31)
	polypharmacy	9,277 (46)	574 (51)
	hyper polypharmacy	1,889 (9)	210 (19)
Number of antihypertensives; N (%)	1	6,708 (34)	347 (31)
	2	6,700 (34)	341 (30)
	3 or more	6,576 (33)	447 (39)
HbA1c in %; mean ± SD		6.9 ± 1.0	7.0 ± 1.0
	missing	976 (5)	62 (5)
Diabetes duration ≥ 10 years; N (%)		5,459 (27)	358 (32)
BMI in kg/m^2; mean ± SD		30.4 ± 5.6	30.4 ± 5.5
	missing	793 (4)	69 (6)
DBP in mmHg; mean ± SD		73 ± 10	71 ± 11
	missing	216 (1)	10 (1)
eGFR ≤ 60 mL/min/1.73m^2; N (%)		4,121 (21)	347 (31)
	missing	4,045 (20)	143 (13)
Smoking; N (%)		2,797 (14)	150 (13)
	missing	4,770 (24)	233 (21)
LDL cholesterol ≥2.5 mmol/L; N (%)		7,259 (36)	421 (37)
	missing	5,718 (29)	298 (26)
Albuminuria; N (%)		396 (2)	21 (2)
	missing	11,913 (60)	630 (56)
Hypotension related adverse event; N (%)			
	Postural hypotension (K88)		534 (47)
	Weakness, tiredness (A04)		336 (30)
	Dizziness, vertigo (N17)		229 (20)
	Syncope (A06)		117 (10)

SBP = systolic blood pressure; HbA1c = glycated hemoglobin A1c; BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; LDL = low-density lipoprotein.

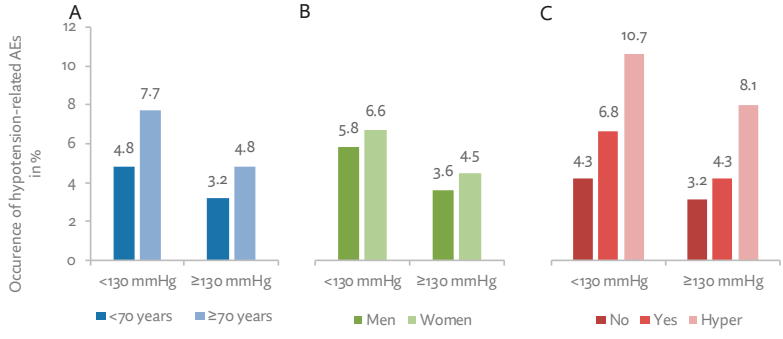
Associations with the occurrence of hypotension-related AEs

Older patients more often experienced a hypotension-related AE than younger patients (6.6% vs. 4.2%; Figure 1A). In the logistic regression analysis, this main effect of age was statistically significant (OR 1.29, 95% CI 1.02-1.64; Figure 2A).

Women more often experienced a hypotension-related AE than men (5.8% vs. 4.9%; Figure 1B), but this difference was not statistically significant (OR 1.06, 95% CI 0.84-1.32; Figure 2B).

Patients prescribed more comedication more often experienced a hypotension-related AE (no polypharmacy 3.8%, polypharmacy 5.8% and hyper polypharmacy 10.0%; Figure 1C). In the logistic regression analyses, the effects of polypharmacy and hyper polypharmacy were statistically significant (OR polypharmacy vs. no polypharmacy 1.27, 95% CI 1.00-1.62 and OR hyper polypharmacy vs. no polypharmacy 2.37, 95% CI 1.67-3.37; Figure 2C).

Patients with SBP levels <130 mmHg more often experienced a hypotension-related AE than those with SBP ≥130 mmHg (6.2% vs. 4.0%; Figure 1). Statistically significant higher occurrence of AEs with lower SBP levels was shown in all conducted analyses (Figure 2): age (OR 1.41, 95% CI 1.14-1.75), sex (OR 1.43, 95% CI 1.17-1.76) and polypharmacy (OR 1.33, 95% CI 1.06-1.67).



SBP at index date (mmHg)*	Age (years)		Sex		Polypharmacy			Total AEs (%)
	<70	≥70	Men	Women	No	Yes	Hyper	
<130	322/6678	480/6203	357/6177	445/6704	225/5232	415/6141	162/1508	6.2
≥130	128/4003	205/4235	146/4035	187/4203	126/3937	159/3710	48/591	4.0
Total AEs (%)	4.2	6.6	4.9	5.8	3.8	5.8	10.0	5.4

Figure 1: Occurrence of hypotension-related adverse events (AEs) per systolic blood pressure (SBP) level by (A) age, (B) sex and (C) polypharmacy. The table below presents the numbers of AEs per total number of patients in that group. *Index date is defined as the lowest SBP level between 2012 and 2014.

Modifying effect of age, sex, and polypharmacy on the occurrence of AEs in patient treated to low SBP level

The interactions between the determinants and SBP level <130 mmHg were not statistically significant (OR for interaction with age 1.01, 95% CI 0.77-1.33 in Figure 2A; OR for interaction with sex 0.98, 95% CI 0.75-1.27 in Figure 2B; OR for interac-

tion with polypharmacy 1.17, 95% CI 0.87-1.56 and OR for interaction with hyper polypharmacy 0.95, 95% CI 0.63-1.42 in Figure 2C). This indicates that older patients, women, and patients with polypharmacy or hyper polypharmacy are not at additional risk of hypotension-related AEs when having SBP levels <130 mmHg than younger patients, men, and patients with no polypharmacy when having low SBP levels.

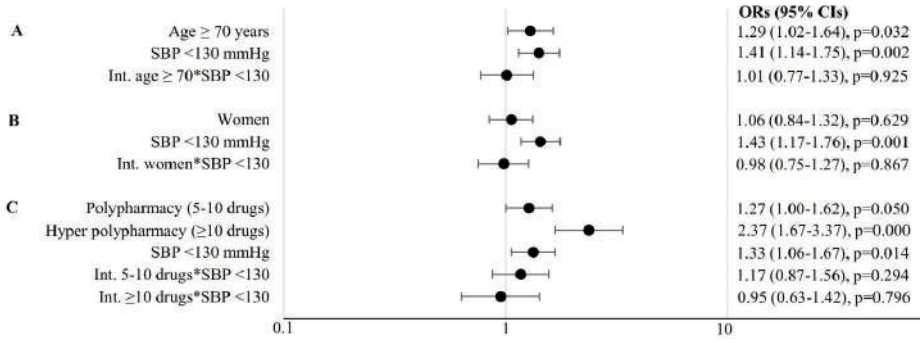


Figure 2: Odds ratios (OR) with 95% confidence intervals (CIs) and p-values for (A) age, (B) sex, (C) polypharmacy, with systolic blood pressure (SBP) and their interactions. Age and sex analyses were adjusted for glycated hemoglobin, diabetes duration, body mass index, smoking, diastolic blood pressure, estimated glomerular filtration rate, glucose lowering therapy, dyslipidemia, lipid lowering therapy, albuminuria, number of comedication and sex or age; polypharmacy analysis was adjusted for the same variables except for glucose and lipid lowering therapy. Int.=interaction

Sensitivity analyses

The sensitivity analysis with a higher cut-off level for age showed that patients aged ≥80 years experienced more hypotension-related AEs than younger patients (7.8% vs. 4.8%), but that this main effect was no longer statistically significant (OR 1.08, 95% CI 0.82-1.41; Figure S2 and S3).

The analysis using an SBP cut-off of 120 mmHg showed similar results as the main analysis (Figure S4 and Figure S5). When using an SBP cut-off of 140 mmHg (Figure S6) the effects of SBP level and age became non-significant (Figure S7). Furthermore, patients with polypharmacy but not with hyper polypharmacy were at an additional risk of hypotension-related AEs at SPB levels <140 mmHg when compared to patients without polypharmacy (polypharmacy OR 1.52, 95% CI 1.02-2.28; hyper polypharmacy OR 1.16, 95% CI 0.66-2.04; Figure S7). None of the other interactions were statistically significant.

Each of the additional AEs in the extended list occurred in 2% to 10% of patients who experienced an AE (Table S1). The analyses including these additional AEs showed similar results as the main analyses (Figure S8 and Figure S9).

DISCUSSION

This study among T2D patients treated with antihypertensives showed that older age, polypharmacy, and low SBP levels were all independently related to experiencing more hypotension-related AEs. The higher occurrence of hypotension-related AEs among patients with low SBP levels was not significantly aggravated by older age, female sex, or polypharmacy.

Several studies in non-diabetic populations have shown a higher occurrence of AEs in older patients (17, 19, 20) and in one study also no significant interaction between age and SBP level on AEs was observed (18). Our results showing a higher occurrence of AEs at older age without an interaction with SBP level are therefore in line with these previous studies.

Nevertheless, a meta-analysis of clinical trials, several of which included T2D patients, showed an increased risk of hypotension in patients younger than 65 years, which they assumed was a consequence of more intensive antihypertensive treatment in younger patients (29). Although they observed slightly higher increment of discontinuations in the older patients, the ratio between risks and benefits was similar in older and younger patients. We found no significant differences in the occurrence of hypotension-related AEs between older and younger patients when using the SBP level 140 mmHg as a cut-off value. Our findings confirm the clinical trial data in a real-world setting of patients with T2D and suggests that lowering SBP levels below 140 mmHg seems safe in patients of all ages. Nevertheless, patients with T2D treated with antihypertensives reaching SBP levels below 130 mmHg should be closely monitored for the occurrence of hypotension-related AEs and possible overtreatment, regardless of age.

In our study, women had a slightly higher occurrence of hypotension-related AEs than men, but this difference was not significant after adjusting for possible confounders. This is not in line with other studies showing increased occurrence of AEs in women (14, 16, 17, 20, 30). Most of these studies, however, used different methods in reporting of AEs and often no adjustments were made for confounding of SBP level or age.

We saw a generally higher occurrence of hypotension-related AEs in patients prescribed more medication, which was independent of the SBP level. This is in line with several studies showing a higher occurrence of AEs in patients prescribed more medication or those with a greater comorbidity burden (17, 18, 30, 31). In one study, also no significant interaction between frailty and SBP levels on AEs was found (18). In itself, the occurrence of hypotension-related AEs in those prescribed more medication was high. Amongst those with hyper polypharmacy, almost 11% of patients with SBP level <130 mmHg and more than 8% of patients with SBP level ≥130 mmHg

experienced a hypotension-related AE. Whether this is due to the actual large number of medication or underlying diseases in unknown, but it can cause a great burden on the healthcare system, the patients' health state and their quality of life. Sufficient attention for negative effects of hypertension treatment in patients with hyper polypharmacy is warranted.

Overall, patients reaching low SBP levels had a higher occurrence of hypotension-related AEs then those with higher SPB levels. This is in line with previous studies and meta-analyses (4, 26, 32, 33). Of note is our finding that this was independent of the patients' age, sex, and number of medications. This implies that attention for hypotension-related AEs is generally required in patients treated to low SBP levels. The occurrence of AEs is a common reason for poor medication adherence (34). To increase the likelihood of adherence to the antihypertensive treatment, possible benefits and risks of treatment should be weighted, and a personalized SBP target should be discussed with the patient (1) and occasionally re-evaluated during treatment. Unless the patient is adequately informed about the benefits and possible AEs of intensive treatment and agrees with it, less intensive treatment with higher SBP targets should be considered.

The strength of our study is using real world data from almost all T2D patients treated in a large number of general practices in the north of the Netherlands. It should be noted that this region consists mostly of Caucasian people. The results may not be generalizable to other populations. Further, we conducted several sensitivity analyses using different age and SBP level cut-offs and AE definitions to validate our findings and further explore the relationship between SBP and the occurrence of hypotension-related AEs. Several limitations mostly related to the use of a database with routinely recorded primary care data must be acknowledged. First, it is possible that the general practitioners were not aware of or did not record all AEs that were experienced by patients, or that there were errors in the coding. A comparison with a recent clinical trial (18) of patients without diabetes showed somewhat similar rates of hypotension (2.5% in our study compared to 1.6% in the clinical trial). For some AEs we observed lower occurrences, for example, syncope (0.6% vs. 1.8%, respectively). In general, we do not expect that the recording of AEs would differ across patients but some patients might report more AEs to their prescribers than others (35). Also, although we selected AEs which are related to hypotension, we cannot guarantee that these AEs were caused by a low SBP level. We conducted a post hoc analysis using only those AEs which occurred at the same time or after the low SBP level was recorded to reduce the chance of the two events not being connected. This analysis revealed similar results (FigS10 and FigS11). Nevertheless, there can be other causes for the AEs, also for the common postural hypotension in our study. Further, the number of SBP measurements varied between patients, with 2% of patients having only one measurement in the

study period. It is not clear to what extent this might bias our findings. Next, some of the included confounders had almost a third of missing values. We used multiple imputation for these variables to reduce possible bias. Furthermore, we included polypharmacy as an indicator of comorbidity. Other measures, such as frailty, were unfortunately not recorded in our data. Last, we did not include the type of drug or drug dose or treatment duration in the analysis. Although this might explain part of the differences in the occurrence of AEs between different subpopulations, this is not expected to affect the associations between the SBP levels and hypotension-related AEs.

To conclude, the observed higher occurrence of hypotension-related AEs in older patients, patients with polypharmacy and those with low SBP levels indicates that there should be sufficient attention for hypotension-related AEs in those patients. Contrary to our expectation, age, sex, and polypharmacy did not increase the risk of hypotension-related AEs associated with a low SBP level in patients with type 2 diabetes. Possible negative effects of medication treatment to low SBP targets in clinical practice should be regularly evaluated in all patients with T2D. Personalized treatment targets may be warranted to reduce hypotension-related AEs, but also other underlying problems and treatment options should be explored with these patients.

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SUPPLEMENTARY MATERIAL

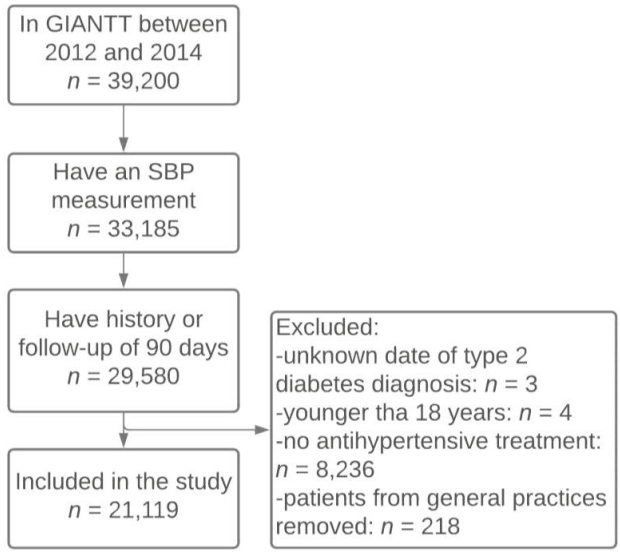
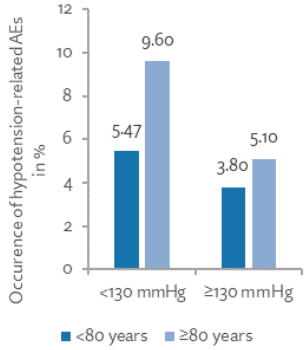


Figure S1: Included patients based on the inclusion criteria. GIANTT = Groningen Initiative to ANalyse Type 2 diabetes Treatment; SBP = systolic blood pressure.

Cut-off 80 years

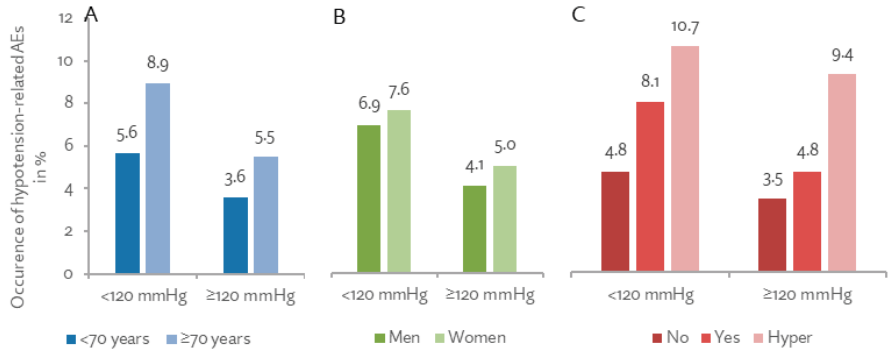


SBP at index date (mmHg)*	Age (years) <80	≥80
<130	576/10528	229/2353
≥130	255/6709	78/1529
AEs (%)	4.8	7.8

Figure S2: Occurrence of hypotension-related adverse events (AEs) per systolic blood pressure (SBP) level for patients aged <80 years and ≥80 years. The table below presents the numbers of AEs per total number of patients in that group. *Index date is defined as the lowest SBP between 2012 and 2014.

Figure S3: Odds ratios (OR) with 95% confidence intervals (CIs) and p-values for age, systolic blood pressure (SBP) and their interaction. This analysis was adjusted for glycated hemoglobin, diabetes duration, body mass index, smoking, diastolic blood pressure, estimated glomerular filtration rate, glucose lowering therapy, dyslipidemia, lipid lowering therapy, albuminuria, number of comedication and sex. Int.=interaction.

Cut-off 120 mmHg



SBP at index date mmHg)*	Age (years) <70	≥70	Sex Men	Women	Polypharmacy No	Yes	Hyper	Total AEs (%)
<120	185/3279	284/3177	211/3057	258/3399	111/2328	255/3166	103/962	7.3
≥120	265/7402	401/7261	292/7155	374/7508	240/6841	319/6685	107/1137	4.5

Figure S4: Occurrence of hypotension-related adverse events (AEs) per systolic blood pressure (SBP) level by (A) age, (B) sex and (C) polypharmacy. The table below presents the numbers of AEs per total number of patients in that group. *Index date is defined as the lowest SBP level between 2012 and 2014.

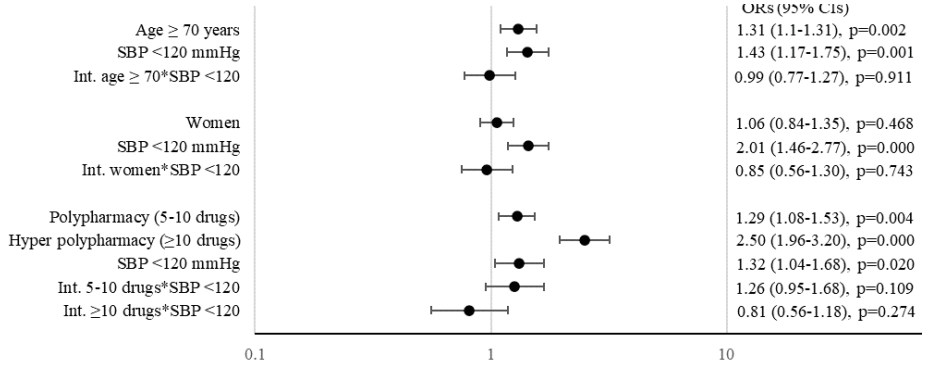
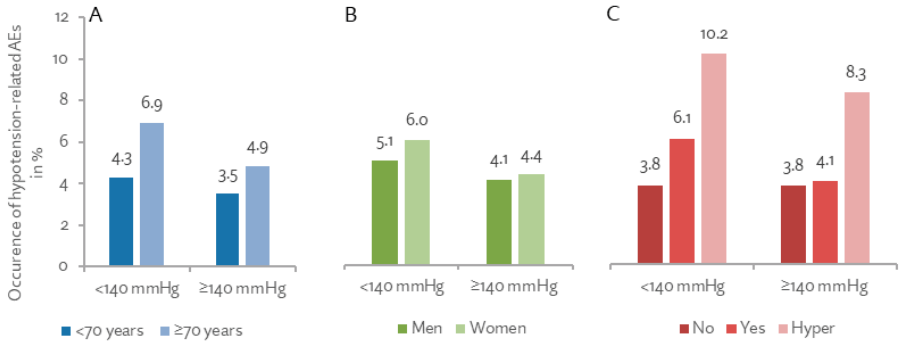


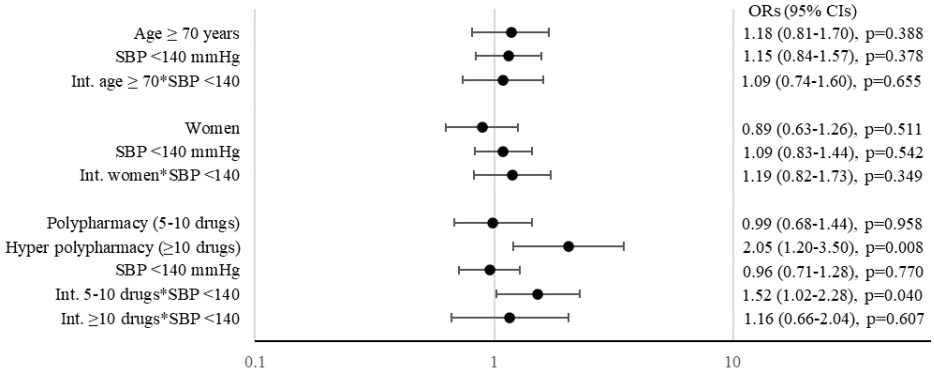
Figure S5: Odds ratios (OR) with 95% confidence intervals (CIs) and p-values for age, sex, polypharmacy, and systolic blood pressure (SBP) and interactions. Age and sex analyses were adjusted for glycated hemoglobin, diabetes duration, body mass index, smoking, diastolic blood pressure, estimated glomerular filtration rate, glucose lowering therapy, dyslipidemia, lipid lowering therapy, albuminuria, number of comedication and sex or age; polypharmacy analysis was adjusted for the same variables except for glucose and lipid lowering therapy. Int.=interaction

Cut-off 140 mmHg



SBP at index date (mmHg)*	Age (years)		Sex		Polypharmacy			Total AEs (%)
	<70	≥70	Men	Women	No	Yes	Hyper	
<140	402/9309	598/8644	440/8689	560/9264	293/7649	517/7928	190/1859	5.6
≥140	48/1372	87/1794	63/1523	72/1643	58/1520	57/1406	20/240	4.3

Figure S6: Occurrence of hypotension-related adverse events (AEs) per systolic blood pressure (SBP) level by (A) age, (B) sex and (C) polypharmacy. The table below presents the numbers of AEs per total number of patients in that group. *Index date is defined as the lowest SBP level between 2012 and 2014.

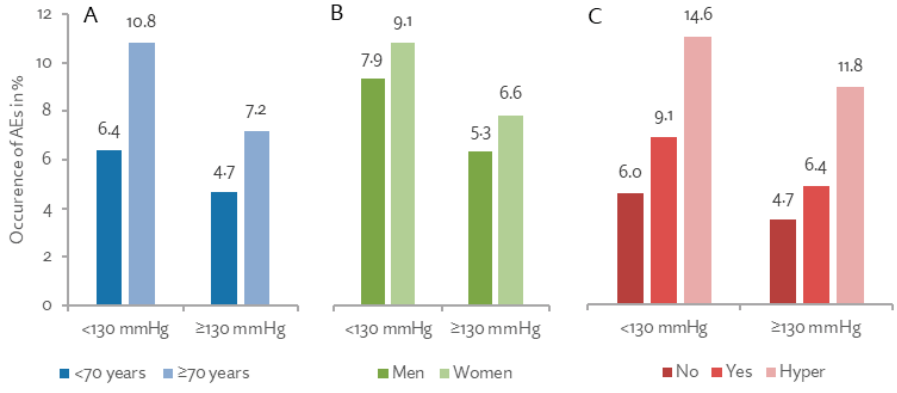


FigS7: Odds ratios (OR) with 95% confidence intervals (CIs) and p-values for age, sex, polypharmacy, and systolic blood pressure (SBP) and interactions. Age and sex analyses were adjusted for glycated hemoglobin, diabetes duration, body mass index, smoking, diastolic blood pressure, estimated glomerular filtration rate, glucose lowering therapy, dyslipidemia, lipid lowering therapy, albuminuria, number of comedication and sex or age; polypharmacy analysis was adjusted for the same variables except for glucose and lipid lowering therapy. Int.=interaction

Sensitivity analysis using an extended list of adverse events

Table S1: Presence of additional adverse events; N (%); N = 1,588

Postural hypotension (K88)	534 (34)
Weakness, tiredness (A04)	336 (21)
Dizziness, vertigo (N17)	229 (14)
Musculoskeletal injury (L81)	166 (10)
Syncope (A06)	117 (7)
Abrasion, scratch (S17)	110 (7)
Trauma, injury (A80)	109 (7)
Other fracture (L76)	87 (5)
Bruises, concussion (S16)	74 (5)
Femur fracture (L75)	27 (2)



SBP at index date (mmHg)*	Age (years)		Sex		Polypharmacy			
	<70	≥70	Men	Women	No	Yes	Hyper	Total AEs (%)
<130	426/6678	670/6203	485/6177	611/6704	316/5232	560/6141	220/1508	8.5
≥130	188/4003	304/4235	215/4035	277/4203	183/3937	239/3710	70/591	6.0
Total AEs (%)	5.8	9.3	6.9	8.1	5.4	8.1	13.8	7.5

Figure S8: Occurrence of hypotension-related adverse events (AEs) per systolic blood pressure (SBP) level by (A) age, (B) sex and (C) polypharmacy. The table below presents the numbers of AEs per total number of patients in that group. *Index date is defined as the lowest SBP level between 2012 and 2014.

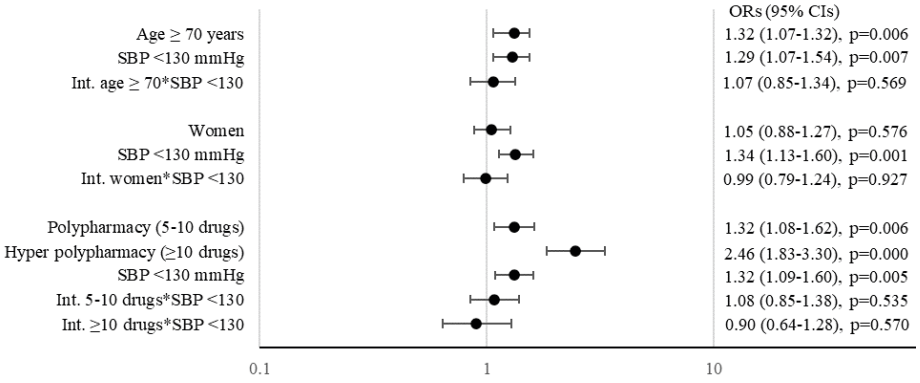
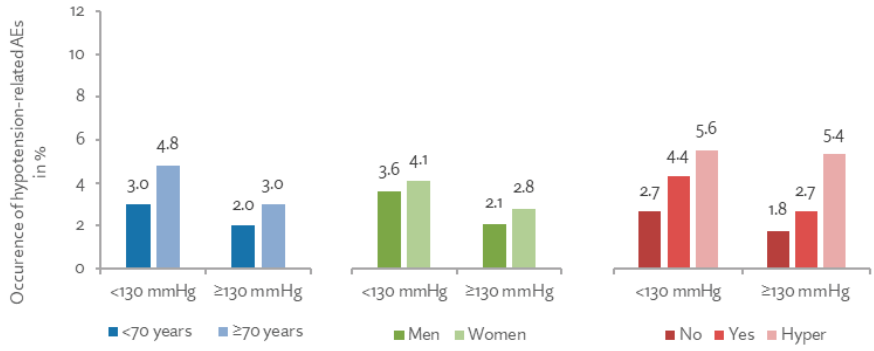


Figure S9: Odds ratios (OR) with 95% confidence intervals (CIs) and p-values for age, sex, polypharmacy, and systolic blood pressure (SBP) and interactions. Age and sex analyses were adjusted for glycated hemoglobin, diabetes duration, body mass index, smoking, diastolic blood pressure, estimated glomerular filtration rate, glucose lowering therapy, dyslipidemia, lipid lowering therapy, albuminuria, number of comedication and sex or age; polypharmacy analysis was adjusted for the same variables except for glucose and lipid lowering therapy. Int.=interaction

Post hoc analysis using only adverse events which occurred in the 90 days after or at the index date



SBP at index date (mmHg)*	Age (years) <70	Age (years) ≥70	Sex Men	Sex Women	Polypharmacy No	Polypharmacy Minor	Polypharmacy Major	Total AEs (%)
<130	203/6678	295/6203	224/6177	274/6704	143/5232	270/6141	85/1508	3.9
≥130	79/4003	126/4235	86/4035	119/4203	72/3937	101/3710	32/591	2.5
Total AEs (%)	2.6	4.0	3.0	3.6	2.3	3.8	5.6	3.3

Figure S10: Occurrence of hypotension-related adverse events (AEs) at or after the index date per systolic blood pressure (SBP) level by (A) age, (B) sex and (C) polypharmacy. The table below presents the numbers of AEs per total number of patients in that group. *Index date is defined as the lowest SBP level between 2012 and 2014.

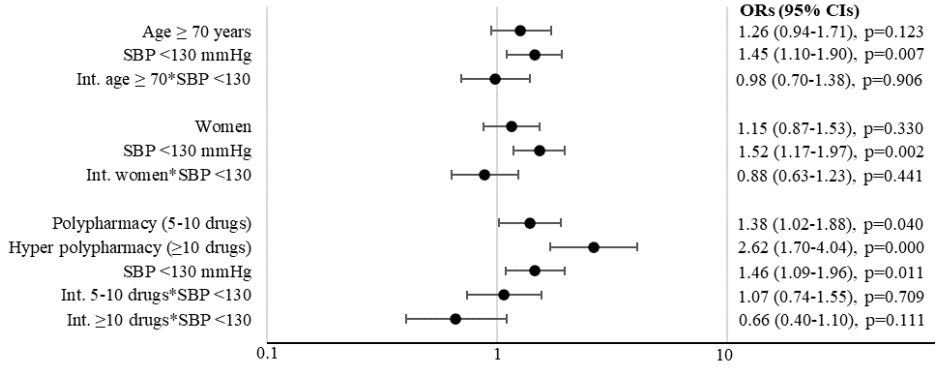


Figure S11: Odds ratios (OR) with 95% confidence intervals (CIs) and p-values for age, sex, polypharmacy, and systolic blood pressure (SBP) and interactions. Age and sex analyses were adjusted for glycated hemoglobin, diabetes duration, body mass index, smoking, diastolic blood pressure, estimated glomerular filtration rate, glucose lowering therapy, dyslipidemia, lipid lowering therapy, albuminuria, number of comedication and sex or age; polypharmacy analysis was adjusted for the same variables except for glucose and lipid lowering therapy. Int.=interaction

9

Discussion

Personalized treatment means that medical decisions are tailored at individual patient characteristics. For the management of type 2 diabetes (T2D) personalized medicine is highly recommended by the guidelines, however it may be difficult to implement in clinical practice. Besides a range of patient characteristics that should be considered, patients' preferences and needs ought to play a major role when making treatment decisions. The majority of studies in this thesis provide insights into the implementation of personalized medicine in primary diabetes care using a database with information from electronic healthcare records. With this, areas for improvement can be identified. Using a patient survey in the final study, more insight was gained into patients' willingness and considerations for engaging in lifestyle changes and medication taking to manage T2D.

In **chapters 2 and 3** we present the trends in glycated haemoglobin A1c (HbA1c) and systolic blood pressure (SBP) thresholds at initiation of glucose- and blood pressure-lowering medication between the years 2007 and 2014. Furthermore, since guidelines started to recommend higher thresholds for older and frail patients from 2011 onwards, we assessed the influence of age and frailty on these trends. Although we observed some changes in thresholds over the years, we did not see the expected differences in thresholds based on age or frailty among the patients with T2D. Since changing prescribing practice might take more time, we assessed these trends for the period of 2015 to 2020 in **chapter 4**. Again, none of the expected differences between patients of different ages were observed in this period. On the contrary, younger patients initiated glucose-lowering treatment at higher thresholds than older patients. So, almost ten years after the introduction of more personalized treatment recommendations, for which the age of the patient is one of the relevant factors, treatment initiation in patients with T2D still appears to lack relevant differentiation. While age is very straightforward to assess and incorporate in decision making, frailty is a more difficult and partly subjective measure, which can best be determined using questionnaires or tests (1). Since the results of such tests were not sufficiently available in the electronic healthcare records, the analysis of frailty was hampered. In addition to age, we aimed to get more insight into potential sex differences, which started gaining more attention in the last years, in **chapter 4**. Interestingly, we observed that males initiated glucose-lowering medication at higher HbA1c thresholds than females, indicating unwanted delays in the start of treatment among males. No sex differences were observed regarding the initiation of blood pressure-lowering medication.

To explore sex differences further, we looked at the disparities in the quality of medication prescribing between males and females with T2D using previously developed prescribing quality indicators in **chapter 5**. We observed that females were significantly less often treated with metformin and renin-angiotensin-aldosterone inhibitors (RAAS-i) when indicated than males. Furthermore, we found that statin

treatment was less often started and prescribed in females than males. All-in-all, this indicates that females with T2D may in part be undertreated for cardiovascular and renal risks. Since the risk of cardiovascular disease differs between patients of different sex, age and menopausal status, we further examined cholesterol levels in relation to sex, age and statin treatment in **chapter 6**. Among patients with T2D not treated with a statin, we observed significantly lower low-density lipoprotein (LDL) cholesterol levels in females at younger ages and higher LDL cholesterol levels in females after the age of 50 years as compared to males. Statin treatment mitigated the observed sex differences at younger ages, however, we still observed higher LDL cholesterol levels in females than males after the age of 55, which might be related to the menopausal status. Independent of statin treatment, we observed higher levels of high-density lipoprotein (HDL) cholesterol in females than males with T2D of all ages, which were previously also observed in the general population. Furthermore, we observed that younger males had significantly higher triglyceride levels than females and older males in this T2D population, which was not mitigated by statin treatment. High triglyceride levels have previously been observed in both the general and diabetic populations, and are of concern since the combination of high triglyceride levels and low HDL cholesterol greatly increases the risk of cardiovascular events.

In **chapter 7** we assessed the association between the occurrence of hypotension-related adverse events (hrAEs) and low SBP levels in patients with T2D treated with blood pressure-lowering medication. We observed that patients with an SBP level <130 mmHg, older patients and patients with polypharmacy were more likely to experience hrAEs than those with higher SBP levels, younger patients and patients without polypharmacy, respectively. We observed no differences in the occurrence of hrAEs between males and females. We also observed that age, sex and polypharmacy did not modify the risks of hrAEs associated with a low SBP level. This indicates that treatment to low SBP levels does not lead to an additional increase in hrAEs risk in older patients, females or patients with polypharmacy.

In the last chapter (**chapter 8**) we present the results from a survey study conducted in the Netherlands and the United Kingdom where we gained insight into patients' willingness to engage in healthy eating, physical activity and medication treatment to manage their T2D, and their considerations and characteristics related to this willingness. We included patients who were recently diagnosed with T2D and found that most of these patients were willing to engage in either a healthy diet, physical activity or take oral medication. However, only half of the patients were willing to engage in all three management options. It became clear that there were meaningful differences between individuals regarding the options that they considered relevant and feasible to implement. Participants from the UK were less willing to follow the proposed recommendations for healthy eating than those from the Netherlands,

while for sufficient physical activity or medication taking, patients with higher overall perceived capabilities, opportunities and motivation were more often willing than those with lower scores. Although participants willing and not willing to engage in a particular management option mentioned similar considerations, those not willing to manage T2D with the suggested recommendations for healthy eating disagreed with the recommendations or believed that other diets were more appropriate, those willing to engage in physical activity perceived less difficulties or barriers to do so and those willing to take medication had more positive and less negative outcome beliefs than those not willing.

Based on the findings of this thesis, the following areas need attention in practice and research:

(a) overtreatment of older and frail T2D patients and those with polypharmacy regarding glucose- and blood pressure-lowering medication,
(b) statin and RAAS-i undertreatment among females with T2D,
(c) delays in glucose-lowering treatment initiation among males and younger T2D patients,
(d) management of high triglycerides among younger male T2D patients,
(e) addressing patients' preferences, beliefs, barriers and needs regarding lifestyle changes and medication treatment when implementing personalized diabetes management.

CONSIDERATIONS OF METHODOLOGIES

For most of the studies in this thesis, the GIANTT database was used. This database includes a large number of patients with T2D from a wide range of general practices in the north of the Netherlands. It provides detailed information about patients' medical history, the drugs prescribed, diagnostic and laboratory measurements, and comorbidities data collected in routine care. The use of such a database also has some limitations. First, due to a mostly Caucasian population in the north part of the Netherlands, the results of our studies may not be representative for other populations. Next, the use of electronic healthcare records results in missing data and misclassifications which might affect the findings. We have tried to address this by using multiple imputation and conducting validation checks. Further, the changing number of general practices and patients included in specific years in the GIANTT database can affect the results when making comparisons over the years, so we conducted several sensitivity analyses. Another aspect that likely influenced some of our results is the COVID-19 pandemic. As observed in chapter 4, HbA1c and SBP thresholds in

2020 increased when compared to previous years. This is possibly a consequence of less regular visits for certain patients with T2D in the beginning of the pandemic (2).

Applying prescribing quality indicators on databases, as done in chapter 5, also merits some reflection. Such quality indicators should not be seen as assessing appropriate prescribing for individual patients. Instead, they are indicators or signals for the extent to which prescribing at population level reflects general guideline recommendations. Depending on the amount of information included in the indicators, they can become more specific. For example, when a guideline recommends prescribing statins in most patients with type 2 diabetes, a 'non-specific' indicator is the proportion of diabetes patients prescribed a statin. A more specific indicator would incorporate information on risk-factor level and prior cardiovascular events. The indicators we used differed in this level of specificity.

Regarding the survey study, several strengths and limitations of online surveys should be acknowledged. The reliability and validity of online obtained data has been shown to be comparable to those obtained with in-person surveys (3, 4). In general, it is easier to include patients from a larger geographic area, it might result in more truthful answers, as well as lower the costs and time as compared to a paper based survey (3, 4). Patients can also fill in the survey at their own time and save it and continue later, which lowers the patient burden (3, 4). There are also some limitations. Despite our survey being piloted to assure its clarity, some questions might be misinterpreted by the participants, which is difficult to check using an online survey. Also, people who do not have access to the internet or do not know how to use it are underrepresented in online survey samples. Finally, due to a recruitment strategy including advertisements with an open questionnaire link we were not able to assess a response rate.

BARRIERS TO THE IMPLEMENTATION OF PERSONALIZED MEDICINE

Personalized medicine does not yet appear to be sufficiently applied in clinical practice, which suggests that the implementation of personalized guideline recommendations is difficult and may take considerable time. Several barriers to the use of clinical practice guidelines have previously been recognized and can be related to the healthcare professionals (e.g. prescribers' knowledge and attitudes), the guidelines or evidence (e.g. lack of convincing evidence or utility), the health system (e.g. implementation process and organisation of care), and the patients (e.g. patients' willingness and preferences) (5, 6). Several of these are relevant for our findings.

Healthcare professionals and guidelines

General practitioners are a crucial stakeholder in the implementation of personalized diabetes treatment. They need to have sufficient knowledge of the guidelines, which might be difficult given the availability of many disease-specific guidelines from various sources, which are updated at different moments in time. For example, the Verenso guideline (7) started to recommend higher HbA1c targets for frail patients in 2011, while the Dutch College of General Practitioners (*Nederlands Huisartsen Genootschap*; NHG) type 2 diabetes guideline (8) did this in 2013. Furthermore, guidelines for nurse practitioners, who are an important team member in diabetes care, are published by other organizations and at different times than those for general practitioners. For example, nurse practitioner guidance (9) still recommended one target for all patients at least three years after personalized guidelines for general practitioners had been published. This can lead to different management strategies and conflicts between members of the same team, and therefore slower implementation of new personalized guidelines.

Second, guideline recommendations for personalized diabetes care have become rather complex. These guidelines may contain many pages of information, which can make them difficult to grasp, especially for practitioners in general practices who encounter a high number of guidelines for different diseases (5, 6). Different interventions to increase the uptake of guidelines have been developed (10-12). In the Netherlands, various organizations develop educational materials and courses, there are decision support tools integrated in the electronic healthcare records, and pharmacotherapy counselling groups in primary care (13-16). The use of these resources is, however, voluntary. Although healthcare professionals must attend a number of educational events each year in order to keep their license, they are free in choosing the diseases and topics. Furthermore, the effects of some resources can be limited. For example, the effect of pharmacotherapy counselling groups depends on their level of functioning (17).

Next, some practitioners might be more successful in guideline and personalized medicine implementation than others, which can be partly related to the use of resources mentioned in the previous paragraph. We did not find big differences between general practices in our studies, but we were not able to distinguish differences at individual practitioner level. Since many practices include several general and nurse practitioners, looking at practice level can mask significant differences between individual practitioners. Therefore, potential differences between practitioners as well as their barriers and facilitators to the implementation of personalized diabetes treatment should be studied further.

Last, healthcare professionals often argue that the guidelines do not fit all patients and that they prefer or need to use their personal judgement when setting individual

treatment targets, which may lead to deviating from the guidelines (5, 6). Since guidelines are mostly based on the results from clinical trials which often exclude certain patients, such as those with comorbidities (18), the applicability of some of the guideline recommendations in clinical practice where many patients have comorbidities might indeed be limited. Frailty of patients adds to this complexity, especially due to different definitions and tools to measure it, as well as different types of frailty which have recently been suggested (1). Since frailty is included in the guidelines but there is no consensus on how to assess it, more research is needed to examine how it is actually used in practice.

Health system and organisation of diabetes care

Most of chronic diabetes management in Dutch primary care is done by nurse practitioners, and is quite protocolized (19). While this type of care is supposed to provide many benefits, such as systematic regular visits, good quality of care, higher patient satisfaction and better support for self-management (20-23), protocolized care has the risk of not addressing each patient's specific needs (24, 25). Ideally, these protocols should incorporate complex rules driven by data of individual patients (26).

Further, patients with T2D may visit multiple healthcare professionals, including general practitioners and nurses, pharmacists, dieticians, and sometimes psychologists. Interprofessional collaboration in diabetes care has shown several benefits, such as access to different intervention programs, improved clinical outcomes, higher patient satisfaction and higher quality of care (27-30). Nevertheless, lack of continuity of care, lack of clear roles, disagreement between healthcare professionals and unintentionally consigning the responsibility of setting and reaching personalized targets to others may result in patients becoming sub optimally treated or confused (27, 31).

Patient influences

Since the patient is highly responsible for the success of the T2D management, their involvement and preferences should play a major role in the management of diabetes. Setting and especially achieving personalized targets is therefore only possible with their involvement. What would be optimal personalized care from the perspective of the clinician, however, is not necessarily what a patient wants. For example, it was found that the beliefs of many older adults about the need for aggressive diabetes treatment did not reflect the personalized guideline recommendations (32). Also, patients can get confused if their target levels change over time or if they get conflicting information about target levels (27, 33). Consequently, they might not agree with the proposed targets and changes in therapy, which makes the implementation of personalized targets difficult. Furthermore, diabetes patients, particularly those with

multimorbidity, might get overwhelmed by guideline-recommended self-care activities and medication taking for all of their risk factors and diseases (34, 35), resulting in poor adherence. In our survey study, participants mentioning lack of time, support and/or motivation as barriers to different diabetes management options. The above mentioned patient concerns and needs should therefore be sufficiently addressed to assure good implementation of personalized medicine.

Although we did not observe the expected age or frailty related differences in medication initiation in our studies, we did see differences in prescribing according to the sex of the patient. Since sex is not included in the current guideline recommendations, it is unclear what the underlying reasons for these differences are. Some could be related to patient differences in behavioural and biological factors, such as differences in patient preferences and the occurrence of side effects (36, 37), but we did not observe sex differences in the willingness to engage in different management options in our survey study.

OPPORTUNITIES FOR IMPLEMENTATION OF PERSONALIZED DIABETES MANAGEMENT

Guideline implementation

First, to increase the dissemination and implementation of guideline recommendations for personalized diabetes management, additional efforts or different strategies seem to be needed. Studies looking at interventions, like audit and feedback, academic detailing and educational games, have shown variable effectiveness in changing prescribing behaviour or improving patient outcomes (38-40). Academic detailing seems better than no educational activities and feedback seems to be most effective when it is provided by colleagues (40), so peer-to-peer support in combination with academic detailing could provide meaningful improvements in the implementation of new personalized guidelines. Based on different areas with the need of improvement, the interventions should probably be multifaceted and should focus on different healthcare professionals. General practitioners may need more education and decision support tools for the management of multimorbid and frail patients. Furthermore, training to provide person-centred care, addressing patients' preferences and needs, is relevant for optimal T2D management. Medication-reviews, conducted or supported by a pharmacist, can help to reduce potential under- and overtreatment (41, 42). Conducting a pharmacist-led medication review tailored for T2D patients showed potential to increase deprescribing and improve appropriate use of cardiometabolic medication (43). A combination of such interventions could

assure better and more personalized quality of care, but further studies are needed to assess the effects in the Dutch healthcare system.

Electronic healthcare record systems

Better use could be made of information which can be stored in electronic healthcare records. A system for clinical rules, alerts, feedback and suggestions has been developed, which is integrated into electronic healthcare records used by general practices in the Netherlands (16). Such a system can be used to suggest personalized targets based on the patient characteristics, as well as provide regular feedback to the prescriber and practice (44). Healthcare professionals can make selections of older patients and monitor on, for example, potential under- or overtreatment. The challenge is to create systems with sufficient specificity to avoid information overload and alert fatigue (45, 46). Furthermore, patients' preferences, perspectives and needs should be better integrated in these systems by patients occasionally answering specific questionnaires, such as those related to frailty, quality of life, needs or medication-related problems they encounter. It has been shown that collecting patient-reported information through questionnaires can improve patient-provider communication, disease control and quality of life (47). In some systems it is possible to document, for example, frailty, side effects or adherence problems with medication, which could be further incorporated in individualized clinical rules. The requirement, however, is that all relevant patient information is indeed documented and updated in the records. For example, a frailty measurement – such as the Groningen Frailty Indicator or the Tilburg Frailty Indicator – should be completed regularly for older patients with T2D and included in clinical rules. A system like this could save time and improve patient care but further studies about its effectiveness and potential cost savings are relevant.

Patient education and support

In order to improve patient involvement and incorporate their views and abilities in an efficient way, patient education might be needed. Although several organizations already provide a laymen's version of the guidelines, educational brochures and information for patients on the internet, these materials are the same for all patients (48-50). Since the needs and preferences of patients for participation in diabetes care are different, more effort in personalized patient support and education might help with its effectiveness and help improve treatment outcomes (51-53). Furthermore, specific nutrition recommendations might not be suitable for all patients (54, 55). So different patients might need different support, but it is unclear how best to implement this in clinical practice. Although patients can be referred to a dietitian or physical therapist which can help them overcome struggles with lifestyle changes and help them find the best management option for them, the barriers identified in our survey

study indicate that this type of support might not yet be sufficiently offered in clinical practice. It has been shown that the involvement of different healthcare professionals into diabetes care can improve the quality of care and help patients with specific problems they encounter on a daily basis, as well as save general practitioners time (56-59). Additionally, sufficient and appropriate patient education and support can improve patient reported and health behaviour outcomes (60-62).

Use of technology for engaging patients

Technology can be an efficient way to engage patients and to incorporate different healthcare professionals in an easier way, lower the costs and improve treatment outcomes (23, 63, 64). A nice example of technology is the MiGuide app (https://miguide.nl/), which has been developed in the Netherlands with the intention to help patients with T2D to change their lifestyle, prevent complications and lower the need for medication. The app motivates patients to be physically active and offers personalized education and suggestions for healthy eating, physical activity, sleep and relaxation. The app can be connected with the healthcare pr0vider to show medical records and gives the general or nurse practitioner access to lifestyle patterns and home measurements, as well as filled out patient questionnaires. The first results of using this app regarding more patient- and goal-oriented care, time saving and patient satisfaction are encouraging (65).

Another eHealth system, currently not available in the Netherlands, is the Joslin HOME model (66), which includes information on several biomarker readings as well as provides communication with a team of healthcare professionals in one system. The patient can choose which professionals they would like to have included in their diabetes management team and which of them are able to schedule appointments when they see needed. The care is provided through virtual or in-person collaborations and communication, and patients can use the support of specific team members when dealing with daily struggles of managing T2D. In a pilot study in the United States of America, this internet-based diabetes model was found to increase the efficiency of visits and improve the HbA1c levels (67).

Further, a European wide initiative called integrated personalized diabetes management (iPDM) strives to implement a six-step disease management process, which provides different digital tools and takes advantage of the data in a structured and individualized way (23). The first results showed improved HbA1c levels as well as higher patient satisfaction, however the system is still in development stages and is yet to be implemented in the clinical care.

Although technology holds the promise of a more efficient way of communication and collaboration (68), limiting factors of systems like this are the loss of patient-physician contact, data privacy issues and challenges for the older population. Also,

integration of these systems in the current healthcare information systems can be difficult.

FUTURE PERSPECTIVES AND FINAL THOUGHTS

We identified several areas regarding the implementation of personalized treatment of T2D in primary care that need attention, particularly related to potential under- and overtreatment of specific populations and the inclusion of patients' preferences and needs when making treatment decisions. Future prospective and qualitative studies would be helpful to get more understanding on why and when personalized medicine is difficult to implement. Furthermore, studies are needed to compare the effectiveness of different implementation strategies, as well as long-term population studies to assess the clinical implications of the observed potential under- and overtreatment. Finally, thought is needed to define the ultimate goal of personalized medicine: is it higher quality of life and patient satisfaction, lower morbidity and mortality, higher cost-effectiveness, or do we need to combine these different goals and preferences into one system? Answering this question will provide us with guidance on future research needs to support personalized medicine into clinical practice.

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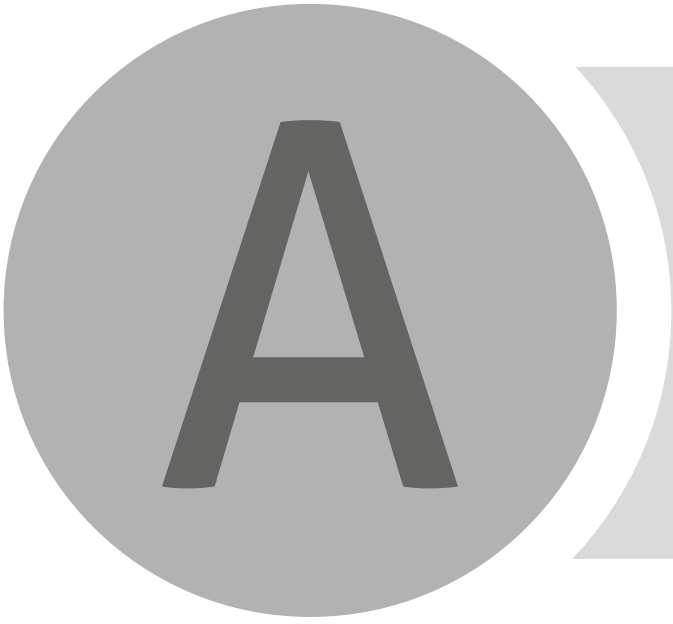
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Appendices

NEDERLANDSE SAMENVATTING

Personalized medicine betekent dat medische beslissingen worden aangepast aan individuele patiëntkenmerken. Voor de behandeling van type 2 diabetes (T2D) wordt *personalized medicine* aanbevolen in de richtlijnen, maar het kan moeilijk zijn om dit altijd in de praktijk toe te passen. Naast een aantal klinische patiëntkenmerken waar rekening mee gehouden moet worden, zijn de voorkeuren en behoeften van patiënten van belang bij het maken van behandelbeslissingen. Verschillende studies in dit proefschrift geven inzicht in de implementatie van *personalized medicine* in de eerstelijns diabeteszorg op basis van informatie uit elektronische patiënten dossiers. Verder is met een vragenlijststudie inzicht verkregen in de bereidheid en overwegingen van patiënten om leefstijl veranderingen toe te passen en medicatie te gebruiken om T2D te behandelen.

In **hoofdstuk 2 en 3** presenteren we de trends in hemoglobine A1c (HbA1c) en systolische bloeddruk (SBD) waarden bij het starten van glucose- en bloeddrukverlagende medicatie in de periode 2007 tot 2014. Daarbij hebben we de invloed van leeftijd en kwetsbaarheid op deze trends geëvalueerd, omdat richtlijnen vanaf 2011 hogere drempelwaarden voor oudere en kwetsbare patiënten adviseerden. Hoewel we enkele veranderingen in drempelwaarden hebben waargenomen, zagen we op basis van leeftijd of kwetsbaarheid geen van de verwachtte verschillen. Omdat veranderingen in de praktijk meer tijd kunnen vergen, hebben we deze trends vervolgens voor de periode 2015 tot 2020 geëvalueerd in **hoofdstuk 4**. Ook in deze periode zagen we geen van de verwachtte verschillen tussen patiënten van verschillende leeftijden. Integendeel, jongere patiënten begonnen met glucoseverlagende behandeling bij hogere drempelwaarden dan oudere patiënten. Bijna tien jaar na de introductie van meer gepersonaliseerde behandeladviezen voor patiënten met T2D, waarbij de leeftijd van de patiënt één van de relevante factoren is, lijkt bij het starten van medicamenteuze behandeling er weinig sprake te zijn van een dergelijke differentiatie. Naast leeftijd wilden we in **hoofdstuk 4** meer inzicht krijgen in potentiële verschillen in behandeling tussen mannen en vrouwen, iets waarvoor in de laatste jaren meer aandacht is. Opvallend was dat mannen bij hogere HbA1c drempelwaarden startten met glucoseverlagende medicatie dan vrouwen. Er waren geen verschillen tussen mannen en vrouwen in het starten van bloeddrukverlagende medicatie.

In **hoofdstuk 5** hebben we de verschillen in kwaliteit van het voorschrijven van medicatie tussen mannen en vrouwen met T2D nader bekeken . We zagen dat vrouwen minder vaak behandeld werden met metformine en renine-angiotensine-aldosteron remmers (RAAS-i) dan mannen. Verder vonden we dat statinebehandeling minder vaak werd gestart en voorgeschreven bij vrouwen dan bij mannen. Dit geeft aan dat

vrouwen met T2D mogelijk onderbehandeld zijn voor cardiovasculaire en renale risico's.

In **hoofdstuk 6** hebben we de cholesterolwaarden in relatie tot geslacht, leeftijd en statinebehandeling onderzocht bij patiënten met T2D. Onder patiënten die niet behandeld werden met een statine, zagen we lagere Lage Dichtheid Lipoproteïnen (LDL) cholesterolwaarden bij vrouwen op jongere leeftijd en hogere LDL cholesterolwaarden bij vrouwen na de leeftijd van 50 jaar in vergelijking met mannen. Dit houdt mogelijk verband met de menopausale status. Met statines waren de verschillen tussen mannen en vrouwen op jongere leeftijd kleiner, maar we zagen nog steeds hogere LDL cholesterolwaarden bij vrouwen dan bij mannen na de leeftijd van 55. Onafhankelijk van statinebehandeling, zagen we hogere waarden Hoge Dichtheid Lipoproteïne (HDL) cholesterol in vrouwen dan in mannen met T2D van alle leeftijden, wat eerder ook in de algemene populatie is waargenomen. Daarnaast zagen we dat jongere mannen hogere triglyceridewaarden hadden dan vrouwen en dan oudere mannen. Dit werd beïnvloed door statinebehandeling.

In **hoofdstuk 7** hebben we de associatie onderzocht tussen het optreden van hypotensie-gerelateerde bijwerkingen (hgAEs) en lage SBD-waarden bij patiënten met T2D die behandeld worden met bloeddrukverlagende medicatie. We zagen dat patiënten met een SBD-waarde <130 mmHg, oudere patiënten en patiënten met polyfarmacie vaker last hadden van hgAEs dan degenen met respectievelijk hogere SBD-waarden, jongere patiënten en patiënten zonder polyfarmacie. We zagen geen verschillen in het optreden van hgAEs tussen mannen en vrouwen. Het risico op hgAEs bij patiënten met een lage SBD-waarde nam niet extra toe door hoge leeftijd, vrouwelijk geslacht of polyfarmacie.

In het laatste hoofdstuk (**hoofdstuk 8**) presenteren we de resultaten van een vragenlijstonderzoek uitgevoerd in Nederland en het Verenigd Koninkrijk onder mensen zie recent de diagnose T2D hebben gekregen. Met de vragenlijst hebben we inzicht gekregen in de bereidheid van patiënten om gezond te eten, fysiek actief te zijn en medicatie te nemen om hun T2D te behandelen. Daarnaast hebben we onderzocht welke overwegingen en gedragsfactoren samenhangen met deze bereidheid. We vonden dat de meeste patiënten bereid waren om een gezond dieet toe te passen of voldoende fysieke actief te zijn of orale medicatie in te nemen. Slechts de helft van de patiënten was echter bereid om alle drie de behandelopties te volgen. Deelnemers uit het Verenigd Koninkrijk waren minder bereid om de voorgestelde aanbevelingen voor gezonde voeding op te volgen dan de Nederlandse deelnemers. Patiënten met een hogere totaalscore op de gedragsfactoren "capaciteit, gelegenheid en motivatie" bleken vaker bereid om voldoende fysiek actief te zijn of medicatie in te nemen dan degenen met lagere scores. Patiënten die weinig bereid waren de voorgestelde aanbevelingen voor gezonde voeding te volgen vonden de aanbevelingen niet passend

of geloofden ze dat andere diëten meer geschikt waren. Degenen die bereid waren om fysieke actief te zijn ervoeren minder moeilijkheden of barrières om dit te doen. Degenen die bereid waren om medicatie te nemen hadden meer positieve en minder negatieve verwachtingen over de effecten daarvan dan degenen die daartoe minder bereid waren.

Gezien de bevindingen is er in de praktijk en in onderzoek specifiek aandacht nodig voor:

(a) overbehandeling met glucose- en bloeddrukverlagende medicatie bij oudere en kwetsbare T2D-patiënten en degenen met polyfarmacie,
(b) onderbehandeling van statines en RAAS-i bij vrouwen met T2D,
(c) het niet tijdig starten van glucoseverlagende behandeling bij manlijke en jongere T2D-patiënten,
(d) behandeling van hoge triglyceriden bij jongere mannelijke T2D-patiënten,
(e) de verwachtingen, barrières en motivatie van patiënten met betrekking tot leefstijlveranderingen en medicatiebehandeling bij de implementatie van gepersonaliseerde diabeteszorg.

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It was about five years ago when I was sitting in my old office having an interview about a PhD position in Groningen, the Netherlands. Not really sure where Groningen is, I found the position in combination with the Prominent program very interesting. Now, after almost five years on a roller coaster which included corona lockdowns, learning statistics, figuring out Stata errors, buying a house and having a baby and two cats, attending national and international conferences, meeting people I can now call good friends, starting a job as a project manager, and so much more, I am ready to close this chapter of finishing a PhD project. It has not been easy, but luckily, I had some great people by my side who helped me make it to the end.

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Martina

ABOUT THE AUTHOR

Martina Ambrož was born on 3rd of November 1989 in Maribor, Slovenia. After completing high school in 2008, she studied Pharmacy at the Faculty of Pharmacy, University of Ljubljana. She successfully defended her Master's thesis with the title ''Postoperative pain management after total knee and hip arthroplasty in University clinical center Maribor.'' in the end of 2014. After working as a sales representative at Pliva Slovenia and as a medical advisor at AbbVie Slovenia between the years of 2015 and 2018, she started working as a PhD student at the Department of clinical pharmacy and pharmacology at the University medical center Groningen in September 2018. During the PhD she presented her work during several national and international conferences in the forms of posters and oral presentations. She started a new job as a Clinical project manager at Tracer in October 2022 and successfully defended her PhD thesis in May 2023.