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**Overtreatment of older patients with type 2 diabetes mellitus in primary care**

Running title: Overtreatment in older type 2 diabetes patients

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## Abstract

There are indications of overtreatment in older type 2 diabetes patients in both the US and Europe. We assessed the level of personalized diabetes treatment for older patients in primary care, focusing on overtreatment.

Based on Dutch guidelines individuals  $\geq 70$  years were classified into three HbA1c treatment target groups: 7% (53 mmol/mol), 7.5% (58 mmol/mol) and 8% (64 mmol/mol).

In our cohort of 1.002 patients ( $n=319 \geq 70$  yrs), the 165 patients with target above 7% had more micro- and macrovascular complications, used more often  $\geq 5$  medicines and were more often frail compared to those with an HbA1c target  $\leq 7\%$ .

Of these 165 patients 64 (38.8%) were overtreated, i.e. 20% of all people  $\geq 70$  years. The majority of overtreated people were frail and used  $\geq 5$  medicines. Hypoglycemia occurred in 20.3% of these patients and almost 30% reported fall accidents.

Personalized treatment in older people with type 2 diabetes is no common practice. A substantial number of older people are overtreated, with likely harmful consequences. To prevent overtreatment, definition of lower HbA1C limits might be helpful.

## 50 **Introduction**

51 Beneficial effects of stringent HbA1c goals in older patients with long existing type 2  
52 diabetes and vascular complications are not proven. On the contrary, older patients  
53 are at higher risk of developing hypoglycemia because of reduced food intake and  
54 wrong medication usage. Hypoglycemia is associated with adverse effects like low  
55 health-related quality of life, development of dementia, cardiovascular disease, falls  
56 and even increased mortality. Overall, the risk of harm associated with an HbA1c  
57 target lower than the conventional 7% (53 mmol/mol) seems to outweigh the possible  
58 benefits for adults of 70 years and older. The American Diabetes Association (ADA)  
59 provides a framework for considering treatment goals for glycemia, with reasonable  
60 HbA1c goals ranging from < 7.5% (58 mmol/mol) to < 8.5% (69 mmol/mol). <sup>1</sup>

61 In 2013, the Dutch College of General practitioners published guidelines, based on  
62 results of the ACCORD, ADVANCE and VADT trials, with an algorithm to put  
63 personalized hyperglycemia treatment into practice. With this algorithm, the  
64 personalized HbA1c target can be determined based on the patient's age, the  
65 intensity of diabetes treatment and the known diabetes duration. <sup>2</sup> According to this  
66 algorithm patients aged  $\geq 70$  years treated with a lifestyle advice only or with  
67 metformin monotherapy should achieve an HbA1c target  $\leq 7\%$  (53 mmol/mol).  
68 Patients above 70 years who are using more blood glucose lowering agents than  
69 metformin only and with a diabetes duration less than 10 years should achieve an  
70 HbA1c  $\leq 7.5\%$  (58 mmol/mol) and those with a diabetes duration above 10 years  
71 have a target  $\leq 8\%$  (64 mmol/mol). In the Netherlands, about 85% of people with type  
72 2 diabetes are treated in the primary care setting. Most recent data (2013) from a  
73 nationwide primary care database provide proportions of type 2 diabetes patients in

primary care < 70 years with an HbA1c < 7% (53 mmol/mol) and an HbA1c > 8.5% (69 mmol/mol).<sup>3</sup> However, these percentages do not provide insight into the level of personalized hyperglycemia treatment. In the US and Europe there are indications of overtreatment in older type 2 diabetes patients, both in patients with and without pre-existing vascular complications.<sup>4-6</sup> We aimed to assess the level of the personalized diabetes treatment for older patients in primary care, focusing on overtreatment.

## **METHODS**

### **Study design and setting**

Data for this observational study (study period January 1<sup>st</sup> – December 31<sup>st</sup> 2016) were extracted from the electronic patient records in March 2017 in five primary care centers of the Leidsche Rijn Julius Health Centers. People were excluded when they were treated for their diabetes by a medical specialist (n=165), refused diabetes care (n=37) or did not show up for monitoring visits during the observation period (n=66), resulting in 1.002 patients with type 2 diabetes included in the study.

### **Data collection and variables**

Patient characteristics, macrovascular- and microvascular complications and comorbidities were all retrieved from the electronic medical records in March 2017, as well as medication use. We defined polypharmacy as the prescription of at least five medications per patient. A person's frailty was determined by the validated Frailty Index (FI).<sup>7</sup> In this study, patients with a FI score >0.2 were considered frail. Data on hypoglycemia, emergency room visits and fall accidents were manually retrieved from the electronic medical records in patients who were classified as overtreated. Hypoglycemia was considered present when patient's complaints due to a low blood glucose level had been recorded.

## Personalized Hba1c targets: on target, overtreatment and undertreatment

According to the algorithm from the Dutch guidelines (Supplementary Appendix, Figure 1) older individuals, i.e.  $\geq 70$  years, could be classified in different subgroups with the accompanying HbA1c target. Based on the differential targets, we defined 'on target', 'overtreated' and 'undertreated' as follows: *If target  $\leq 7\%$  (53 mmol/mol):* no lower limit available for overtreatment, on target if HbA1c  $\leq 7\%$  (53 mmol/mol), undertreated if HbA1c  $> 7\%$  (53 mmol/mol); *if target  $\leq 7.5\%$  (58 mmol/mol):* overtreated if HbA1c  $\leq 7\%$  (53 mmol/mol), on target if HbA1c  $> 7\%$  (53 mmol/mol) but  $\leq 7.5\%$  (58 mmol/mol), undertreated if HbA1c  $> 7.5\%$  (58 mmol/mol); *if target  $\leq 8\%$  (64 mmol/mol):* overtreated if HbA1c  $\leq 7\%$  (53 mmol/mol), on target if HbA1c  $> 7\%$  (53 mmol/mol) but  $\leq 8\%$  (64 mmol/mol), undertreated if HbA1c  $> 8\%$  (64 mmol/mol).

## Statistical Analyzes

Patients on their personalized treatment targets were compared to those not on treatment target using Chi-square, Mann Whitney U and Kruskal Wallis tests (IBM SPSS statistics 24).

## RESULTS

In the cohort the mean age was 62.8 (12.2) years, with 54.1% men and a median diabetes duration of 7.0 years (36.2%  $\geq 10$  years). The median HbA1c was 6.9% (52 mmol/mol), 20.3% of the patients had macrovascular complications and 38.2% had microvascular complications. Of the 1.002 patients, 319 (31.8%) patients were  $\geq 70$  years with 51.7% men and a median diabetes duration of 10 years. Their median HbA1c was 7.0% (53.3 mmol/mol), 30.1% had macrovascular complications and 50.8% had microvascular complications. One in five people  $\geq 70$  years used insulin

and almost 70% in this age category used at least five medications (Supplementary Table). Using the algorithm from the Dutch guidelines, 165 people could be classified in the subgroup with an HbA1c target  $> 7\%$  (53 mmol/mol) (Figure 1, Suppl. Appendix). Their median HbA1c was 7.3% (56 mmol/mol, IQR 15) versus 6.8% (51 mmol/mol, IQR 12) in the group with an HbA1c target  $\leq 7\%$  (53 mmol/mol) ( $p < 0.05$ ). Those with an HbA1c target  $> 7\%$  (53 mmol/mol) had more often microvascular (54.0 % vs 35.2%,  $p < 0.05$ ) and macrovascular complications (33.3% vs 17.7%,  $p < 0.05$ ). They used more often  $\geq 5$  medications (87.3% vs 53.2%,  $p < 0.05$ ) and were more often frail (44.2% vs 13.9%,  $p < 0.05$ ) than people with an HbA1c target  $\leq 7\%$  (53 mmol/mol).

Fifty three individuals were categorized in the subgroup with HbA1c target  $\leq 7.5\%$  (58 mmol/mol) and 112 in the subgroup with target  $\leq 8\%$  (64 mmol/mol). In the former subgroup 13 (24.5%) people were on target, 23 (43.4%) were overtreated and 17 (32.1%) undertreated. In the latter group these proportions were 36.6%, 36.6% and 26.8% respectively.

Table 1 shows the characteristics of people with HbA1c treatment target  $\leq 7.5\%$  (58 mmol/mol) and whether they were on target, over- or undertreated. The achieved HbA1c values between these categories differed significantly, but other characteristics did not. More than 80% used sulphonylureas, 15 to 35% used insulin combined with oral blood glucose lowering agents. Almost all people used at least five medications, almost half of them had comorbidities and one in three were frail.

Table 2 provides similar data from the people with HbA1c treatment target  $\leq 8\%$  (64 mmol/mol). Also in this category achieved HbA1c levels differed significantly between people on target, those who were over- and undertreated. Individuals who were 'on target' had significantly less microvascular complications compared to those who

were over- or undertreated (34.1% vs 63.4 % and 66.7%;  $P<0.05$ ). Surprisingly, people who were overtreated used less often insulin combined with oral medication compared to the other two categories (24.4% versus 43.9% and 63.3%,  $p<0.05$ ).

## **Overtreatment**

Overall, 64 people received overtreatment, that means 38.8% of the 165 with an HbA1c target  $> 7\%$  (53 mmol/mol). As stated above 23 (43.4%) of people with HbA1c target  $\leq 7.5\%$  (58 mmol/mol) could be categorized as overtreated according to the evidence based guidelines. They had a median age of 72 years, a median diabetes duration of 5 years and a median HbA1c of 6.5% (48 mmol/mol). Five (21.7%) had an eGFR  $< 45$  ml/min. Eight individuals who were overtreated (34.8%) were living alone and eight (34.8%) were frail. The majority of these overtreated patients used metformin (78.3%) and/ or sulphonylureas (87.0%). Four (17.4%) of them experienced hypoglycemia in the observation period, four had a fall accident and one patient had a hypoglycemia related emergency room visit.

Among the people with an HbA1c target  $\leq 8\%$  (64 mmol/mol) more than one in three (36.6%) patients could be categorized as overtreated. They had a median age of 76 years, a median diabetes duration of 14 years and a median HbA1c of 6.5% (47 mmol/mol). Three (7.3%) had an eGFR  $< 45$  ml/min. Half of the overtreated individuals could be considered frail and 13 (31.7%) lived alone. The majority used metformin (82.9%) and/or sulphonylureas (70.7%). In this group, more people used insulin compared to overtreated individuals with a target  $\leq 7.5\%$  (31.7% vs. 8.7%). During the observation period 12 people (29.3%) reported fall accidents, 9 (22%) reported hypoglycemia and one patient had a hypoglycemia related emergency room visit.



## Discussion

This study aimed to assess the level of personalized type 2 diabetes treatment for older patients in primary care, focusing on overtreatment of these patients. From 319 people  $\geq 70$  years, more than one in two should have an HbA1c target  $> 7\%$  (53 mmol/mol) according to the evidence-based guidelines. Many people who were overtreated according to the guidelines had complications, comorbidities, polypharmacy, can be considered frail and used medication that can cause hypoglycemia.

Although the Dutch diabetes guidelines are very well implemented in primary care, without financial incentives to drive HbA1c levels lower, de-intensifying treatment is not yet common practice, whereas a great number of patients would benefit from it<sup>6,8</sup>. Notably, although hypoglycemia and falls were reported and recorded for overtreated people in our study, their treatment was not de-intensified. Whereas the number of patients included in this study is small, the results give a clear signal that overtreatment in older type 2 diabetes patients is a real problem.

Some limitations should be taken into account. First, no data were available of people who were treated by specialists. Their treatment can be seen as more complex and on the one hand they are less likely to reach their HbA1c target but on the other hand many of them are likely to benefit from a less strict HbA1c target. Also people refusing regular diabetes care could not be included. With these two categories of patients included, the proportion of people receiving overtreatment would have been different.

To conclude, almost 40% of older adults with type 2 diabetes and an evidence based HbA1c target above 7% were overtreated, representing about 20% of all

199 adults  $\geq 70$  years. Also according to the ADA and EASD guidelines they should have  
200 been treated less intensively. Naturally, if a well-informed patient prefers to continue  
201 his or her medication, a shared decision could be to do so. From a medical point of  
202 view such a patient might be called overtreated, but in a person-centered diabetes  
203 care this is acceptable.

204 Care professionals should leave the 'one size fits all' approach and realize the  
205 possible benefits of de-intensifying blood glucose lowering treatment. To prevent  
206 overtreatment, a lower HbA1c limit in the guidelines might be helpful. Diabetes quality  
207 indicators should not be based on population based mean values, because means  
208 will overlook under- and overtreatment completely.

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### 214 **Authors contributions**

215 HEH designed the study, collected data, wrote the manuscript and takes the  
216 responsibility for the manuscript, GEHM designed the study and reviewed the  
217 manuscript, KNB collected and analyzed data, and wrote the first version of the  
218 manuscript, RCV designed the study, analyzed the data and reviewed the  
219 manuscript.

### 220 **Financial disclosure**

221 No funding was received for this study. This study was conducted as part of a  
222 scientific internship during the last year of medical school of KNB.

### 223 **Ethics**

224 Ethical approval was not obtained since this was an observational study with routine  
225 care patient data, anonymously provided.

### 226 **Conflict of interest**

227 The authors state that they have no conflict of interest

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