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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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26 **Abstract**

27

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

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

34 In our cohort of 1.002 patients ( $n=319 \geq 70$  yrs), the 165 patients with target above  
35 7% had more micro- and macrovascular complications, used more often  $\geq 5$   
36 medicines and were more often frail compared to those with an HbA1c target  $\leq 7\%$ .  
37 Of these 165 patients 64 (38.8%) were overtreated, i.e. 20% of all people  $\geq 70$  years.  
38 The majority of overtreated people were frail and used  $\geq 5$  medicines. Hypoglycemia  
39 occurred in 20.3% of these patients and almost 30% reported fall accidents.

40 Personalized treatment in older people with type 2 diabetes is no common practice.

41 A substantial number of older people are overtreated, with likely harmful  
42 consequences. To prevent overtreatment, definition of lower HbA1C limits might be  
43 helpful.

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## 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

74 primary care < 70 years with an HbA1c < 7% (53 mmol/mol) and an HbA1c > 8.5%  
75 (69 mmol/mol).<sup>3</sup> However, these percentages do not provide insight into the level of  
76 personalized hyperglycemia treatment. In the US and Europe there are indications of  
77 overtreatment in older type 2 diabetes patients, both in patients with and without pre-  
78 existing vascular complications.<sup>4-6</sup> We aimed to assess the level of the personalized  
79 diabetes treatment for older patients in primary care, focusing on overtreatment.

80

## 81 **METHODS**

### 82 **Study design and setting**

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

### 89 **Data collection and variables**

90 Patient characteristics, macrovascular- and microvascular complications and  
91 comorbidities were all retrieved from the electronic medical records in March 2017,  
92 as well as medication use. We defined polypharmacy as the prescription of at least  
93 five medications per patient. A person's frailty was determined by the validated Frailty  
94 Index (FI).<sup>7</sup> In this study, patients with a FI score >0.2 were considered frail.

95 Data on hypoglycemia, emergency room visits and fall accidents were manually  
96 retrieved from the electronic medical records in patients who were classified as  
97 overtreated. Hypoglycemia was considered present when patient's complaints due to  
98 a low blood glucose level had been recorded.

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

100 According to the algorithm from the Dutch guidelines (Supplementary Appendix,  
101 Figure 1) older individuals, i.e.  $\geq 70$  years, could be classified in different subgroups  
102 with the accompanying HbA1c target. Based on the differential targets, we defined  
103 'on target', 'overtreated' and 'undertreated' as follows: *If target  $\leq 7\%$  (53 mmol/mol):*  
104 *no lower limit available for overtreatment, on target if HbA1c  $\leq 7\%$  (53 mmol/mol),*  
105 *undertreated if HbA1c  $> 7\%$  (53 mmol/mol); *if target  $\leq 7.5\%$  (58 mmol/mol):*  
106 *overtreated if HbA1c  $\leq 7\%$  (53 mmol/mol), on target if HbA1c  $> 7\%$  (53 mmol/mol)*  
107 *but  $\leq 7.5\%$  (58 mmol/mol), undertreated if HbA1c  $> 7.5\%$  (58 mmol/mol); *if target  $\leq$*   
108 *8% (64 mmol/mol): overtreated if HbA1c  $\leq 7\%$  (53 mmol/mol), on target if HbA1c*  
109  *$> 7\%$  (53 mmol/mol) but  $\leq 8\%$  (64 mmol/mol), undertreated if HbA1c  $> 8\%$  (64*  
110 *mmol/mol).***

## 111 **Statistical Analyzes**

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

115

## 116 **RESULTS**

117 In the cohort the mean age was 62.8 (12.2) years, with 54.1% men and a median  
118 diabetes duration of 7.0 years (36.2%  $\geq 10$  years). The median HbA1c was 6.9% (52  
119 mmol/mol), 20.3% of the patients had macrovascular complications and 38.2% had  
120 microvascular complications. Of the 1.002 patients, 319 (31.8%) patients were  $\geq 70$   
121 years with 51.7% men and a median diabetes duration of 10 years. Their median  
122 HbA1c was 7.0% (53.3 mmol/mol), 30.1% had macrovascular complications and  
123 50.8% had microvascular complications. One in five people  $\geq 70$  years used insulin

124 and almost 70% in this age category used at least five medications (Supplementary  
125 Table). Using the algorithm from the Dutch guidelines, 165 people could be classified  
126 in the subgroup with an HbA1c target > 7% (53 mmol/mol) (Figure 1, Suppl.  
127 Appendix). Their median HbA1c was 7.3% (56 mmol/mol, IQR 15) versus 6.8% (51  
128 mmol/mol, IQR 12) in the group with an HbA1c target ≤ 7% (53 mmol/mol) (p<0.05).  
129 Those with an HbA1c target > 7% (53 mmol/mol) had more often microvascular  
130 (54.0 % vs 35.2%, p<0.05) and macrovascular complications (33.3% vs 17.7%, p<  
131 0.05). They used more often ≥ 5 medications (87.3% vs 53.2%, p<0.05) and were  
132 more often frail (44.2% vs 13.9%, p<0.05) than people with an HbA1c target ≤ 7%  
133 (53 mmol/mol).

134 Fifty three individuals were categorized in the subgroup with HbA1c target ≤ 7.5% (58  
135 mmol/mol) and 112 in the subgroup with target ≤ 8% (64 mmol/mol). In the former  
136 subgroup 13 (24.5%) people were on target, 23 (43.4%) were overtreated and 17  
137 (32.1%) undertreated. In the latter group these proportions were 36.6%, 36.6% and  
138 26.8% respectively.

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

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

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

152

### 153 **Overtreatment**

154 Overall, 64 people received overtreatment, that means 38.8% of the 165 with an  
155 HbA1c target  $> 7\%$  (53 mmol/mol). As stated above 23 (43.4%) of people with  
156 HbA1c target  $\leq 7.5\%$  (58 mmol/mol) could be categorized as overtreated according to  
157 the evidence based guidelines. They had a median age of 72 years, a median  
158 diabetes duration of 5 years and a median HbA1c of 6.5% (48 mmol/mol). Five  
159 (21.7%) had an eGFR  $< 45$  ml/min. Eight individuals who were overtreated (34.8%)  
160 were living alone and eight (34.8%) were frail. The majority of these overtreated  
161 patients used metformin (78.3%) and/ or sulphonylureas (87.0%). Four (17.4%) of  
162 them experienced hypoglycemia in the observation period, four had a fall accident  
163 and one patient had a hypoglycemia related emergency room visit.

164 Among the people with an HbA1c target  $\leq 8\%$  (64 mmol/mol) more than one in three  
165 (36.6%) patients could be categorized as overtreated. They had a median age of 76  
166 years, a median diabetes duration of 14 years and a median HbA1c of 6.5% (47  
167 mmol/mol). Three (7.3%) had an eGFR  $< 45$  ml/min. Half of the overtreated  
168 individuals could be considered frail and 13 (31.7%) lived alone. The majority used  
169 metformin (82.9%) and/or sulphonylureas (70.7%). In this group, more people used  
170 insulin compared to overtreated individuals with a target  $\leq 7.5\%$  (31.7% vs. 8.7%).  
171 During the observation period 12 people (29.3%) reported fall accidents, 9 (22%)  
172 reported hypoglycemia and one patient had a hypoglycemia related emergency room  
173 visit.



174

## 175 **Discussion**

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

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

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

197 To conclude, almost 40% of older adults with type 2 diabetes and an evidence  
198 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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211

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213

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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