Glycemic control and use of glucose-lowering medications in hospital-admitted type 2 diabetes patients over 80 years

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Treatment guidelines for type 2 diabetes (T2D) recommend avoidance of hypoglycemia and less stringent glycemic control in older patients. We examined the relation of glycemic control to glucose-lowering medications use in a cohort of patients aged >80 years with a diagnosis of T2D and a hospital admission in the Capital Region of Denmark in 2012–2016. We extracted data on medication use, diagnoses, and biochemistry from the hospitals’ records. We identified 5,172 T2D patients with high degree of co-morbidity and where 17% had an HbA1c in the range recommended for frail, comorbid, older patients with type 2 diabetes (58–75 mmol/mol (7.5–9%)). Half of the patients (n = 2,575) had an HbA1c < 48 mmol/mol (<6.5%), and a majority of these (36% of all patients) did not meet the diagnostic criteria for T2D. Of patients treated with one or more glucose-lowering medications (n = 1,758), 20% had HbA1c-values < 42 mmol/mol (<6%), and 1% had critically low HbA1c-values < 30 mmol/mol (<4.9%). In conclusion, among these hospitalized T2D patients, few had an HbA1c within the generally recommended glycemic targets. One third of patients did not meet the diagnostic criteria for T2D, and of the patients who were treated with glucose-lowering medications, one-fifth had HbA1c-values suggesting overtreatment.

For patients with type 2 diabetes, it is important to maintain blood glucose levels as close to normal as possible in order to reduce the risk of micro- and macrovascular complications1–4. Treatment should, however, be individualized according to comorbidities, disease duration, risk of adverse events and in particular hypoglycemia, life expectancy as well as the patient’s own preferences, resources and support system1. Elderly people with type 2 diabetes will generally have co-existing illness and relatively few resources5. Life expectancy will often be shorter than the time it takes for micro- and macrovascular disease complications to develop and manifest6,7. This is in contrast to the potential adverse effects of glucose-lowering medications that often appear in the short term. Hypoglycemia is the most important example of an acute and potentially fatal adverse effect to which elderly are particularly vulnerable8–15. Less effective counterregulatory mechanisms, decreased drug elimination, motor and cognitive impairment as well as unspecific/uncharacteristic symptoms all contribute to the heightened risk in elderly patients16. Thus, the overall goal with treatment individualization should be to weigh the typically long-term benefits vs. therapy burden and risk of adverse events on the shorter term7,15,17,18. Available evidence from the few clinical trials enrolling elderly patients with type 2 diabetes support that the benefits of intensive glycemic control targeting near-normal glycemia may not outweigh potential risks in this population19–22. This is also reflected in several international guidelines which generally advocate a less stringent treatment approach for older people with coexisting illnesses. An HbA1c target of 58–75 mmol/mol (7.5–9%) after pharmacological intervention, is generally recommended1,6,7,17. Recent studies have, however, questioned the extent to which these recommendations have been adopted and implemented in clinical practice23,24.

Previous studies examining trends in use, effects (glycemic control as measured by HbA1c) and harms (e.g. hypoglycemia) of glucose-lowering medications have predominantly focused on the general type 2 diabetes population25–29. This study focuses on a cohort of patients aged 80 years or older with a diagnosis of type 2 diabetes.
and a hospital-based health record in the period 2012–2016. The main objective was to examine glycemic control in relation to use of glucose-lowering medications; secondary objectives included characterizing the patient cohort with regards to comorbidity, drug administration and biochemical status at the time of hospital admission.

Results
Patient characteristics and admission diagnoses. A total of 5,172 patients with type 2 diabetes were included in the study (Table 1). The median age was 84 years (IQR 82–88 years) and 54% of the patients were female. Based on Body Mass Index (BMI), 41% were normal weight (BMI 18.5–25 kg/m²) and 55% were overweight or obese (BMI >25 kg/m²) (Table 1). Regarding biochemical status, LDL-cholesterol was >2.5 mmol/L for 25% of the patients. The estimated glomerular filtration rate (eGFR) was ≤60 mmol/L for 57% of the patients and 56% had a hemoglobin below the reference level calculated for men and women respectively (Table 1). The median duration of hospital admission was four days with pneumonia being the most common cause of admission (4%, n = 211). Diabetes related diagnoses were registered as the primary cause of admission for 2% (n = 78) of all patients and 1% (n = 70) had hypoglycemia as the primary cause of admission.

Comorbidities. The majority (82%, n = 4,228) of patients had a high level of comorbidity with a value >2 on the Charlson Comorbidity Index (Table 1). Detailed data on the cognitive status of the patients was not available, but 16% had a diagnosis of dementia (Table 2). Hypertension was the most commonly registered comorbidity (71%), followed by congestive heart failure (32%), peripheral vascular disease (18%) and previous myocardial infarction (13%) (Table 2).

Glycemic control. The distribution of HbA1c values is shown in Fig. 1. Most patients (91%, n = 4,710) had an HbA1c between 30–75 mmol/mol (4.9–9%). Half of the patients (n = 2,575) had an HbA1c <48 mmol/mol (<6.5%), and 26% (n = 1,361) had an HbA1c <42 mmol/mol (<6%). In the other end of the spectrum, 8% (n = 405) had HbA1c-values >75 mmol/mol (>9%) (Table 1). A total of 17% (n = 891) had an HbA1c between 58–75 mmol/mol (7.5–9%), i.e. within the interval recommended for elderly, comorbid patients with overt type 2 diabetes (Table 1).

Glucose-lowering medications. Close to one third of patients (34%, n = 1,758) were treated with at least one glucose-lowering medication at discharge (Table 3); 41% (n = 2,100) were administered at least one glucose-lowering medication, including sliding scale bolus insulin, during the index hospital admission (data not shown). Among the patients treated with glucose-lowering medication at discharge, one fourth (25%, n = 448) were treated with two or more glucose-lowering medications (Table 3). The most commonly used glucose-lowering medications were metformin (50%), basal insulin (32%), bolus insulin (10%), sulphonylureas (14%) and dipeptidyl peptidase-4 inhibitors (14%) (Table 4). One percent (n = 15) of the patients treated with an glucose-lowering medication at discharge had very low Hba1c-values (<30 mmol/mol (<4.9%)) (Table 3, Fig. 1).

For those patients who did not receive a glucose-lowering medication at discharge (n = 3,414), 55% (n = 1,865) had Hba1c-values that did not justify a diagnosis of type 2 diabetes (i.e. HbA1c <48 mmol/mol (<6.5%)) (Table 3, Fig. 1). At the other end of the spectrum, 7% (n = 223) had Hba1c levels for which glucose-lowering medications are generally recommended (i.e.>75 mmol/mol (9%)).

Discussion
Based on hospital electronic health records covering the entire population of the Capital Region of Denmark (1.8 million inhabitants) from 2012 to 2016, we investigated the demographics and the degree of glycemic control in relation to glucose-lowering medications in patients with type 2 diabetes aged 80 years or more. Our main findings were (1) almost half of the patients had an HbA1c <48 mmol/mol (<6.5%), and of these 72% (n = 1,865, 36% of all patients) were not treated with a glucose-lowering medication and thus did not fulfill the diagnostic criteria for type 2 diabetes; (2) of the patients treated with one or more glucose-lowering medications (often including insulin and/or sulphonylureas), 20% had HbA1c-values below 42 mmol/mol (6%) and 1% had critically low HbA1c-values <30 mmol/mol (<4.9%), indicating overtreatment. Conversely, 8% of all patients had Hba1c values >75 mmol/mol (>9%), indicating possible undertreatment.

A surprising finding was that based on HbA1c-value, 36% (n = 1,865) of all the admitted patients did meet the criteria for their diagnosis of type 2 diabetes. The diagnoses were all registered by a physician authorized in Denmark and could have been registered many years prior to the index admission. Thus, one potential explanation for our finding could be that type 2 diabetes is not a chronic disease but rather a condition that may in some cases remit with old age – a notion that has been proposed before32,33. Hence, Abdelhafiz et al. proposed that frailty among older people with type 2 diabetes might lead to the remission of type 2 diabetes with the suggested mechanisms being weight loss accompanied by reduced amounts of visceral fat and thereby improved insulin sensitivity32. Such a mechanism bears resemblance to that described for patients having bariatric surgery and/or substantial weight loss and afterwards experience remission of their type 2 diabetes34,35.
Table 1. Patient characteristics for all patients with type 2 diabetes ≥80 years included in the study. Values are displayed in absolute numbers, percentages and median (inter-quartile range). For haemoglobin and creatinine, the reference values are displayed for men and women separately.
We report that only 17% of included patients had an HbA1c between 58–75 mmol/mol (7.5–9%), the interval generally recommended for elderly with significant comorbidities and limited life expectancy. That our patients were indeed highly comorbid is evidenced by the Charlson comorbidity score, where 94% scored 2 or more. Of those with an HbA1c <42 mmol/mol (<6.0%), 25% were treated with one or more glucose-lowering medications. These findings are in line with findings from other studies that have raised concerns about the potential overtreatment of older people with type 2 diabetes. Among these is a large register-based study by Tseng et al. including 652,738 patients from the Veteran Health Administration. They reported that approximately 50% of patients aged 75 years or older, who were treated with insulin and/or sulphonylureas, had an HbA1c <53 mmol/mol (<7%). Similarly, results from The Fremantle Diabetes Cohort Study, which included 367 patients over the age of 75 with type 2 diabetes showed that approximately three of five (61%) of the patients had an HbA1c <53 mmol/mol (<7%). As treatment needs to be individualized according to a patient's preferences and resources as well as life expectancy it is of interest that in our cohort dementia was registered as a diagnosis for 16% and non-skin malignancy for 19% of the included patients. Studies of frail patients with type 2 diabetes and limited life expectancy, such as nursing home residents, have suggested that particularly elderly with dementia are overtreated with glucose-lowering medications. Thus, in a nursing home population, 46–74% of the patients had an HbA1c <53 mmol/mol (<7%). Although the distributions of HbA1c-values in the mentioned nursing home studies were similar to ours, cognitive and functional impairment may be more frequent in the nursing home setting. One percent (n=70) of our population had hypoglycemia as the primary cause of admission. However, this is likely an underestimate of the number of patients at high risk of hypoglycemia. In older people, hypoglycemia can go undiscovered and be difficult to recognize due to unspecific symptoms. Thus, the substantial proportion of patients, who in the context of near-normal HbA1c (i.e. below 42 mmol/mol (6%)) continued treatment with a sulphonylurea (n=70) or insulin (n=82) could be considered at high risk of hypoglycemic events. Thus, our study adds to the evidence suggesting that the recommendations favoring looser glycemic control in elderly, comorbid people similar to our population has not been fully adopted into clinical practice.

Our study has important strengths such as the large sample size, the high data quality from rather accurate national registers with the possibility of linking biochemical data with health record data and drug use. Nonetheless, this register-based study also has some limitations. In our study, only 34% of elderly patients with a diagnosis of type 2 diabetes were treated with glucose-lowering medications. Other studies on glycemic control in older people, including the mentioned studies of nursing home residents and larger cohort studies report a much higher proportion of patients treated with glucose-lowering medication. Thus, between 85–100% of the patients received glucose-lowering medication in other cohort studies of a general population with type 2 diabetes, and up to 86% were pharmacologically treated in studies investigating glycemic control in nursing home residents. Our lower treatment prevalence is most likely due to the fact that many patients in our cohort did not meet the criteria for type 2 diabetes at the time of study. Since our study was based on a cohort identified by a hospital admission, and data analyses were limited to the time around hospital admission, we did not have information on the duration of diabetes or the glycemic control and use of anti-diabetic medication over time. Access to this information could have strengthened our interpretation particularly the reason for the high proportion of patients not fulfilling the diagnostic criteria for type 2 diabetes. There is some indication that our cohort does not fully reflect the population in the capital region of Denmark. Thus, in our cohort, 54% were female, while the concurrent female proportion in the general population was 65%. The reason for such relative underrepresentation of females in our cohort is unclear. Another issue is that 56% had a hemoglobin below reference level, which theoretically could lead to an underestimation of the HbA1c-values. However, as proposed by samples from another Danish population, mild to moderate anemia does not seem to have significant impact on the interpretation of HbA1c-values.

### Table 2. Number of patients with co-morbidities, using all available data for each individual.

| Co-morbidities              | n (%)       |
|-----------------------------|-------------|
| Hypertension                | 3648 (71%)  |
| Atrial fibrillation         | 1990 (38%)  |
| Congestive heart failure    | 1650 (32%)  |
| Cerebrovascular disease     | 1547 (30%)  |
| Chronic pulmonary disease   | 1207 (23%)  |
| Moderate to severe renal disease | 1079 (21%) |
| Non-skin malignancy         | 984 (19%)   |
| Peripheral vascular disease | 930 (18%)   |
| Dementia                    | 831 (16%)   |
| Myocardial infarction       | 689 (13%)   |
| Thyroid disorders           | 524 (10%)   |
| Depression                  | 455 (9%)    |
| Peptic ulcer disease        | 400 (8%)    |
| Rheumatologic disease       | 137 (3%)    |
| Metastatic solid tumor      | 124 (2%)    |
| Moderate or severe liver disease | 41 (1%)   |
| Schizophrenia               | 10 (0%)     |

We found that only 17% of included patients had an HbA1c between 58–75 mmol/mol (7.5–9%), the interval generally recommended for elderly with significant comorbidities and limited life expectancy. That our patients were indeed highly comorbid is evidenced by the Charlson comorbidity score, where 94% scored 2 or more. Of those with an HbA1c <42 mmol/mol (<6.0%), 25% were treated with one or more glucose-lowering medications. These findings are in line with findings from other studies that have raised concerns about the potential overtreatment of older people with type 2 diabetes. Among these is a large register-based study by Tseng et al. including 652,738 patients from the Veteran Health Administration. They reported that approximately 50% of patients aged 75 years or older, who were treated with insulin and/or sulphonylureas, had an HbA1c <53 mmol/mol (<7%). Similarly, results from The Fremantle Diabetes Cohort Study, which included 367 patients over the age of 75 with type 2 diabetes showed that approximately three of five (61%) of the patients had an HbA1c <53 mmol/mol (<7%). As treatment needs to be individualized according to a patient’s preferences and resources as well as life expectancy it is of interest that in our cohort dementia was registered as a diagnosis for 16% and non-skin malignancy for 19% of the included patients. Studies of frail patients with type 2 diabetes and limited life expectancy, such as nursing home residents, have suggested that particularly elderly with dementia are overtreated with glucose-lowering medications. Thus, in a nursing home population, 46–74% of the patients had an HbA1c <53 mmol/mol (<7%). Although the distributions of HbA1c-values in the mentioned nursing home studies were similar to ours, cognitive and functional impairment may be more frequent in the nursing home setting. One percent (n=70) of our population had hypoglycemia as the primary cause of admission. However, this is likely an underestimate of the number of patients at high risk of hypoglycemia. In older people, hypoglycemia can go undiscovered and be difficult to recognize due to unspecific symptoms. Thus, the substantial proportion of patients, who in the context of near-normal HbA1c (i.e. below 42 mmol/mol (6%)) continued treatment with a sulphonylurea (n=70) or insulin (n=82) could be considered at high risk of hypoglycemic events. Thus, our study adds to the evidence suggesting that the recommendations favoring looser glycemic control in elderly, comorbid people similar to our population has not been fully adopted into clinical practice.

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In this hospital-based cohort consisting of more than 5000 patients, few patients ≥80 years with type 2 diabetes had an HbA1c within the limits generally recommended for this population. Many patients were not treated with glucose-lowering medications and had HbA1c-values that could not justify a diagnosis of type 2 diabetes.

Figure 1. Distribution of individual HbA1c-values for patients with type 2 diabetes >80 years with and without glucose-lowering medications divided into HbA1c-categories. HbA1c-values on the x-axis are displayed in both percentage and in mmol/mol. (a) Displays HbA1c-values for all patients (n = 5172). (b) Displays HbA1c-values for patients treated with glucose-lowering medications (n = 1758).

Table 3. Number of patients grouped by number of glucose-lowering medications administered at the time of hospital discharge and HbA1c-value (obtained ±90 days before hospital admission). HbA1c-values are divided into categories and displayed in mmol/mol.
Danish Data Protection Agency (BFH-2016–058, I-Suite nr.: 04906) and The Danish Patient Safety Authority retrospective register-based studies do not require ethical approval in Denmark. The study was approved by The

comorbidity burden and has been shown to be correlated with life expectancy36.

ate patient comorbidity, we used diagnoses to calculate The Charlson Comorbidity Index, which is a measure of

Exposure and comorbidity. Exposure to a glucose-lowering medication was defined as an active prescrip-

tion of a glucose-lowering medication (Anatomical Therapeutic Chemical classification (ATC)-code A10) at the

time of discharge from the hospital and with at least one administration during the hospital admission. To evaluate

patient comorbidity, we used diagnoses to calculate The Charlson Comorbidity Index, which is a measure of comorbidity burden and has been shown to be correlated with life expectancy40.

Statistical methods. Data are presented using standard descriptive statistics including median and inter-

quartile ranges. Data management was conducted using R46.

Ethics. According to the Danish "Act on Research Ethics Review of Health Research Projects" section 14 (2), retrospective register-based studies do not require ethical approval in Denmark. The study was approved by The Danish Data Protection Agency (BFH-2016–058, I-Suite nr.: 04906) and The Danish Patient Safety Authority (3-3013-1884/1).

Compliance with ethics guidelines. This article is based on previously conducted health data and does not contain any studies with human participants or animals performed by any of the authors.

Data availability

The dataset used in this study is not available due to local law.

Received: 29 August 2019; Accepted: 27 January 2020;

Published online: 05 March 2020

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### Table 4. Antidiabetic medication at the time of hospital discharge in relation to HbA1c-values (obtained ±90 days before hospital admission) for very old patients with type 2 diabetes. Values are displayed in absolute numbers. HbA1c-values are divided into categories and displayed in mmol/mol. Patients count more than once if administered more than one kind of antidiabetic. DPP-4i: dipeptidylpeptidase-4 inhibitor, SGLT-2i: sodium-glucose cotransporter-2 inhibitor, SU: sulfonylurea, GLP-1RA: Glucagon-like peptide-1 receptor agonist.

| Type of glucose-lowering medication | HbA1c category | <30 | 30–41 | 42–47 | 48–52 | 53–57 | 58–74 | 75+ | Total |
|-----------------------------------|----------------|-----|-------|-------|-------|-------|-------|-----|-------|
| Acarbose                          |                | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (100%) | 0 (0%) | 0 (0%) | 2 (100%) |
| Basal Insulin                     |                | 1 (0%) | 51 (9%) | 64 (11%) | 75 (13%) | 79 (14%) | 188 (33%) | 105 (19%) | 563 (100%) |
| Bolus Insulin                     |                | 3 (2%) | 26 (15%) | 23 (14%) | 21 (12%) | 28 (17%) | 44 (26%) | 24 (14%) | 169 (100%) |
| DPP-4i                            |                | 2 (1%) | 30 (12%) | 56 (22%) | 34 (13%) | 36 (14%) | 56 (22%) | 38 (15%) | 252 (100%) |
| GLP-1 RA                          |                | 0 (0%) | 5 (16%) | 7 (23%) | 7 (23%) | 1 (3%) | 10 (32%) | 1 (3%) | 31 (100%) |
| Metformin                         |                | 10 (1%) | 204 (21%) | 254 (26%) | 163 (17%) | 110 (11%) | 169 (17%) | 75 (8%) | 985 (100%) |
| SGLT-2i                           |                | 0 (0%) | 2 (12%) | 1 (6%) | 2 (12%) | 4 (24%) | 6 (35%) | 2 (12%) | 17 (100%) |
| SU                                |                | 4 (2%) | 66 (26%) | 53 (21%) | 40 (16%) | 26 (10%) | 48 (19%) | 16 (6%) | 253 (100%) |
| Total                             |                | 20 (1%) | 384 (17%) | 458 (20%) | 342 (15%) | 286 (13%) | 521 (23%) | 261 (11%) | 2272 (100%) |
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Acknowledgements

The study was funded by the Department of Clinical Pharmacology, Bispebjerg and Frederiksberg Hospital, University of Copenhagen.

Author contributions

D.R.G. and S.V. contributed to drafting of the manuscript and data analyses. T.S.P., T.B.J. and R.C. contributed to study design and data analyses. E.J.S. and M.C. designed the study and contributed to data analyses and manuscript drafting. All authors edited and approved the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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