

## Brief Research Report

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# In-hospital management of type 2 diabetes in Denmark is inconsistent with international guidelines

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### ABSTRACT

**INTRODUCTION.** Insulin is the preferred treatment for hyperglycaemia in hospitalised patients with type 2 diabetes mellitus (T2DM). However, which insulin regimen to prefer is debated. We described Danish regional guidelines on the management of non-critically ill hospitalised patients with T2DM and compared them with international guidelines.

**METHODS.** The Danish regional guidelines have been obtained via Danish regional web portals and by request to the regions. The guidelines were reviewed independently by the authors of this article to ensure uniformity in the interpretation of their contents.

**RESULTS.** The recommended treatment of in-hospital hyperglycaemia is sliding scale insulin (SSI) in all five Danish regions. Insulin dosing by SSI is adjusted to bodyweight in two of the five regions. The recommended number of daily glucose point-of-care tests ranges from 4-8 to reach glucose levels of 5-10 mmol/l (90-180 mg/dl). In all regions, continuation of out-hospital insulin and non-insulin antidiabetic drugs is recommended; however, the latter is paused on wide indications.

**CONCLUSIONS.** In-hospital hyperglycaemia for non-critically ill hospitalised patients with T2DM is treated by SSI, based on short-acting insulin, in all five Danish regions. International guidelines recommend a basal-bolus or basal-plus regimen based on both short- and long-acting insulin for most hospitalised non-critically ill patients with diabetes and discourage SSI. Danish regions should consider replacing SSI with a basal-bolus or basal-plus regimen.

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In Denmark, 10-15% of hospitalised patients have type 2 diabetes mellitus (T2DM) [1]. Glycaemic dysregulation during hospitalisation is associated with increased mortality, morbidity, and length of hospital stay [2, 3]. Independently of a diagnosis of diabetes, most hospitalised patients should therefore maintain blood glucose levels of 5-10 mmol/l (90-180 mg/dl).

For decades, insulin has been the cornerstone in hyperglycaemia treatment of hospitalised patients with diabetes in Denmark and abroad. However, which insulin regimen should be preferred is debated [4].

Historically, the sliding scale insulin (SSI) regimen has been used in non-intensive care units. SSI is based on short-acting insulin. The dose of insulin administered is determined by the glucose level by point-of-care (POC) testing, often performed pre-prandially three times daily, before bedtime, and at night or at fixed time points in fasting patients. Randomised controlled trials have consistently shown superior glycaemic control with insulin regimens based on basal insulin, i.e. long-acting insulin, compared with SSI. This has led to criticism of SSI in leading international diabetes guidelines by the American Diabetes Association, the European Society, and the American Association of Clinical Endocrinologists [5-7]. Instead, these guidelines recommend (based on the highest level of evidence) a basal-bolus regimen for most hospitalised patients with T2DM. The basal-bolus regimen consists of a total daily insulin dose of 0.3-0.5 IU/kg. Half of the total daily insulin dose is given as basal insulin (e.g., glargine) at a fixed time of the day. The other half is given as equally divided pre-prandial doses of bolus insulin, i.e. short-acting insulin (e.g., insulin aspart). Corrective doses of insulin (e.g., insulin aspart) are given depending on the glucose levels.

We aimed to describe which (insulin) regimens are recommended for non-critically ill hospitalised patients with T2DM in the five regions of Denmark and compare these regimens with international guidelines. Furthermore, we assessed which insulin types are recommended, how often glucose should be measured, compared glucose targets, and whether to continue out-hospital antidiabetic drugs or not during hospitalisation.

## METHODS

Four out of five guidelines were obtained via the Danish regional web portals [8-11] and one by request to the region [12]. The guidelines were reviewed independently by the authors of this article to ensure a uniform interpretation of the guidelines.

*Trial registration:* not relevant.

## RESULTS

SSI is recommended for treating in-hospital hyperglycaemia in all five Danish regions. Insulin dosing (often insulin aspart) by SSI is adjusted to bodyweight in two of the regions [8, 9]. The number of daily recommended POC glucose tests range between four and eight times in the five regions to reach glucose target levels of 5-10 mmol/l (90-180 mg/dl). Continuing out-hospital non-insulin antidiabetic drugs and insulin are recommended. The latter, however, is paused on wide indications (**Table 1**). **Table 2** presents the recommended units of insulin at different glucose levels in SSI regimens of the five Danish regions. The Capital Region of Denmark [8] and Region Zealand [9] follow the same SSI regimen, which is similar to that of the Central Denmark Region [11] in regard to initiating SSI at glucose levels of 10 mmol/l (180 mg/dl). The North Denmark Region [10] initiates SSI at glucose levels of 12 mmol/l (216 mg/dl) and the Region of Southern Denmark [12] initiates SSI at glucose levels of 4 mmol/l (72 mg/dl). The authors of this article have reached the same interpretation of the guidelines.

**TABLE 1** Recommended in-hospital hyperglycaemia regimens for non-critically ill patients with type 2 diabetes in all five Danish regions.

Region	Regimen	Insulin type	Population, n	Guideline updated, year	Weight-based?	Daily glucose POC tests, n	Target glucose range, mmol/l (mg/dl)	Out-hospital		
								non-insulin antidiabetic drugs	basal insulin	bolus (meal) insulin
Capital Region of Denmark [8]	SSI	Aspart	1,840,000	2021	Yes	5	5-10 (90-180)	Continued, however, discontinued on wide indication, e.g., vomiting	Continued, however, discontinued during fasting	No information
Region Zealand [9]	SSI	Aspart	840,000	2019	Yes	5	5-10 (90-180)	Continued, however, discontinued during fasting	Continued, however, discontinued during fasting	Continued, however, discontinued during fasting
North Denmark Region [10]	SSI	Aspart	590,000	2022	No	5	No information	Continued No information on when to discontinue	Continued No information on when to discontinue	Continued No information on when to discontinue
Central Denmark Region [11]	SSI	No information	1,320,000	2020	No	4-7	7-10 (130-180)	Continued, however, discontinued on wide indication: intercurrent disease	Continued Reduced or discontinued during fasting or low glucose levels	Continued, however, discontinued during fasting
Region of Southern Denmark [12]	SSI	Aspart	1,220,000	2019	No	5-8	No information	Continued, however, discontinued during fasting	Continued, however, discontinued during fasting	Continued, however, discontinued during fasting

POC = point of care; SSI = sliding scale insulin.

**TABLE 2** Recommended units of insulin at different glucose levels in the sliding scale insulin regimens in all five regions of Denmark.

Glucose level, mmol/l (mg/dl)	Units of insulin					
	Capital Region of Denmark [8] and Region Zealand [9]			North Denmark Region [10]	Central Denmark Region [11]	Region of Southern Denmark [12]
	bodyweight < 60 kg	bodyweight 60-90 kg	bodyweight > 90 kg			
< 4 (< 72)	0	0	0	0	0	0
4-8 (72-144)	0	0	0	0	0	2
< 10 (< 180)	0	0	0	0	0	-
8-12 (144-216)	-	-	-	0	-	4
10-12 (180-216)	2	4	6	0	2	4
10-14 (180-252)	2	4	6	0	-	-
12-16 (216-288)	-	-	-	4	4	6
14-18 (252-324)	3	6	8	-	-	-
16-20 (288-360)	-	-	-	6	6	8
> 18 (> 324)	4	8	10	-	-	8
> 20 (> 360)	4	8	10	8	10	8

## DISCUSSION

We found that all five Danish regions (comprising 5.8 million people) recommend treating hyperglycaemia in non-critically ill hospitalised patients with T2DM by SSI [5-7]. However, international guidelines recommend a basal-bolus regimen for most hospitalised patients with diabetes. In patients with T2DM, the basal-bolus regimen has demonstrated lower mean glucose levels and a higher percentage of glucose levels within the target range of glucose levels < 7.8 mmol/l (< 140 mg/dl) than SSI [13, 14]. In one randomised controlled trial, the basal-bolus regimen decreased the risk of a composite outcome of post-operative wound infection, pneumonia, bacteraemia, acute kidney injury, and respiratory failure in general surgery patients compared with SSI [14].

Although effective in preventing and correcting hyperglycaemia, the basal-bolus regimen is associated with an increased risk of hypoglycaemia than SSI. In-hospital hypoglycaemia is costly and increases in-hospital

morbidity and mortality. In a meta-analysis from 2017 [15], the relative risk of hypoglycaemia on a basal-bolus regimen compared with SSI was 5.8 (95% confidence interval (CI): 2.8-11.8) for glucose levels  $\leq 3.9$  mmol/l ( $\leq 70$  mg/dl) and 4.2 (95% CI: 1.6-11.0) for glucose levels  $\leq 3.3$  mmol/l ( $\leq 60$  mg/dl). The risk of hypoglycaemia for glucose levels  $\leq 2.2$  mmol/l ( $\leq 40$  mg/dl) was not significantly different between the basal-bolus and SSI regimens. However, six out of 633 patients in the meta-analysis experienced hypoglycaemia for glucose levels  $\leq 2.2$  mmol/l ( $\leq 40$  mg/dl), all on a basal-bolus regimen. All studies included in the meta-analysis used POC to measure glucose levels. Continuous glucose monitoring, measuring glucose levels every 1-15 minutes, detects more hypoglycaemic episodes, especially nocturnal hypoglycaemia, since POC is rarely performed during the nighttime [16].

Due to the increased risk of hypoglycaemia with a basal-bolus regimen, SSI may be appropriate in patients with mild stress hyperglycaemia without diabetes [4]. For patients with diabetes and mild hyperglycaemia, patients with diabetes and decreased oral nutritional intake, or surgical patients with diabetes, a basal-plus regimen might be preferred [4]. The basal-plus regimen is based on the same principles as the basal-bolus regimen with basal insulin and corrective doses of insulin but without fixed doses of prandial bolus insulin.

The basal-bolus and the basal-plus regimens are labour-intensive due to the many required insulin administrations. This may contribute to Danish guidelines being reluctant to adopt these internationally endorsed regimens. Fear of (severe) hypoglycaemia might also be a barrier to the implementation of regimens based on long-acting insulin in otherwise out-hospital insulin-naive patients with diabetes. Also, in-hospital diabetes management is often burdened by clinical inertia in regard to changing or adjusting insulin regimens, perhaps translating into a lack of implementation of new guidelines [17].

Switching from the previously used bolus human insulin (e.g., actrapid) to insulin aspart with a lower duration of action further actualises the introduction of basal insulin. In countries with healthcare systems that may be considered comparable to Danish healthcare, i.e. Canada [18], Australia [19] and European countries [20] (Germany, France, Hungary, Poland and the United Kingdom), a basal-bolus regimen or similar regimens relying on long-acting insulins are the recommended and the most applied regimens (applied in 70-80% of patients) for in-hospital management of non-critically ill patients with T2DM [18-20].

## CONCLUSIONS

In-hospital hyperglycaemia is treated by SSI in all five Danish regions. We recommend that Danish regions consider replacing SSI with the internationally recommended basal-bolus regimen or basal-plus regimen for most non-critically ill hospitalised patients with T2DM. The implementation should be accompanied by systematic monitoring of the occurrence of unintended events related to the insulin regimens.

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