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Efficacy and feasibility of basal–bolus insulin regimens and a discharge-strategy in hospitalised patients with type 2 diabetes – the HOSMIDIA study

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SUMMARY

Aims: Guidelines recommend use of basal–bolus insulin in hospitalised patients with hyperglycaemia, but information about implementation and medication reconciliation at discharge is scarce. The HOSMIDIA study evaluated a management program involving basal–bolus insulin and an algorithm for medication reconciliation at discharge in non-critically ill hospitalised patients with type 2 diabetes in clinical practice. **Methods:** HOSMIDIA was a prospective, observational study performed during routine clinical practice at 15 Spanish hospitals during hospitalisation, with follow-up 3 months postdischarge. Study patients ($n = 134$) received a basal–bolus regimen with insulin glargine during hospitalisation and treatment at discharge was adjusted according to a simple algorithm. The control group ($n = 62$) included patients with similar characteristics hospitalised during the month before study initiation and had no follow-up after discharge. **Results:** Compared with control subjects, patients in the prospective study achieved lower mean total (167.7 ± 41.1 vs. 190.5 ± 53.3 mg/dl) preprandial (164.2 ± 42.4 vs. 189.6 ± 52.6 mg/dl; $p < 0.001$) and fasting (137.0 ± 42.2 vs. 165.8 ± 56.5 mg/dl) blood glucose levels while hospitalised, without increased hypoglycaemic episodes (17.7% vs. 19.3% patients). In the prospective study, glycaemic control improved from admission to discharge, with control maintained 3 months after discharge. The main treatment modification at discharge compared with admission was addition of basal insulin, and treatment at discharge was maintained at 3 months in 89% of patients. **Conclusion:** The HOSMIDIA study confirmed that management of hyperglycaemia with basal–bolus insulin is feasible and effective in routine clinical practice, and that a simple strategy facilitating the reconciliation of medication on discharge can improve glycaemic control postdischarge.

What's known
Randomized controlled trials have shown basal–bolus insulin provides better glycemic control in non-critically ill hospitalized patients with T2DM compared with sliding scale insulin. This has led to changes to guidelines, which now recommend use of basal–bolus insulin in this population. Currently, there is no guidance on treatment decisions at discharge and no studies, to which we are aware, have reported the application of these guidelines in clinical practice.

What's new
This study demonstrates that using a basal–bolus regimen in routine clinical practice in non-critically ill patients with type 2 diabetes is feasible and reduces hyperglycemia without increasing the risk for hypoglycemia during hospitalization. In addition, it shows that it is possible to improve glycemic control post-discharge by adjusting treatment at discharge, particularly in those requiring insulin therapy.

Introduction

Worldwide, diabetes is a major cause of mortality and morbidity, and the number of people with diabetes is increasing (1). People with diabetes are more likely to be hospitalised owing to comorbidities of the condition (2,3). Hyperglycaemia, because of decompensated diabetes mellitus, unrecognised diabetes mellitus or hospital-related hyperglycaemia, is considered a common, serious and costly problem in hospitalised patients (4–6). In addition, the transition from hospital to home is one of the most crucial transitions in care. It involves a transfer in responsibility from the inpatient provider to the patient and primary care physician, and is a vulnerable period of discontinuity and potential adverse events, most commonly adverse drug events (7–9).

Observational and randomised controlled studies indicate that improvement in glycaemic control results in lower rates of hospital complications in medical and surgery patients (9,10). Therefore, it is important to treat and prevent hyperglycaemia in the hospital setting and to reconcile the medication that the patient was using before admission with the medication prescribed on discharge, to potentially improve both clinical outcomes and safety (4). Current guidelines (5,9,11,12) recommend avoiding oral antidiabetic drugs (OADs) in hospitalised

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patients, and using standardised insulin protocols with scheduled subcutaneous injection of insulin, with basal, nutritional and correctional components, in non-critically ill patients. Furthermore, they emphasise the importance of continuity of care between inpatient and outpatient settings, and the reconciliation of the medication that the patient was using before admission with the medication prescribed on discharge.

There is data from randomised clinical trials demonstrating that inpatient diabetes management programs involving basal—bolus insulin are effective and well tolerated (13–17). However, information about the implementation of a basal–bolus regimen in clinical practice, is scarce and the transition of diabetes care from the inpatient to outpatient setting is also understudied. This study, therefore, aims to evaluate the feasibility and efficacy in clinical practice of a protocol to manage hyperglycaemia with a basal–bolus insulin regimen using the long-acting insulin analogue insulin glargine as the basal component and a rapid-acting insulin analogue for the prandial and correctional components in non-critically ill hospitalised patients with type 2 diabetes (12). In addition, a strategy to facilitate medication reconciliation on discharge was evaluated.

Methods

Study design

The HOSMIDIA study was a prospective, uncontrolled, observational study performed during routine clinical practice. It was conducted at 15 Spanish hospitals across Spain during hospitalisation, with a follow-up visit 3 months after discharge. Patients were monitored and treated during routine clinical practice while hospitalised, with data recorded every 24 h. The study was approved by local institutional review boards and ethics committees and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All participants in the prospective study group gave informed consent.

Participants

Non-critically ill male and female individuals aged 18 years or older with a documented diagnosis of type 2 diabetes and a planned duration of hospitalisation of at least 3 days in a haemodynamically stable situation were included consecutively in the study. These patients were treated with a basal–bolus regimen that included subcutaneous insulin glargine during hospitalisation. The main exclusion criteria were a diagnosis of type 1 diabetes, admission to hospital for decompensation of diabetes, any psychiatric or neurological disability preventing follow-up, critical illness and participation in any other study.

Data for individuals with similar characteristics (non-critically ill male and female patients aged 18 years or older with type 2 diabetes and at least 3 days of hospitalisation in a haemodynamically stable situation) who had been treated with subcutaneous insulin and were hospitalised during the month before the initiation of the study were recorded retrospectively and consecutively as a control group. The number of patients included in the control group should be no less than one-third of the study group to allow for comparative analysis.

Study treatment (prospective group)

Study treatment was based upon current local treatment guidelines (12). The protocol included three meals, and treatment with basal (insulin glargine) and prandial/correctional insulin (rapid-acting insulin). If an individual used ≥ 2 doses of insulin at home, the total daily dose administered prior to hospitalisation was continued and adjusted as necessary, otherwise the initial total insulin dose recommended was – 0.4 U/kg/day. If an individual was transitioned from continuous intravenous insulin to subcutaneous basal–bolus insulin, whole daily insulin requirement was calculated as 80% of the projected 24-h requirement, calculated on the basis of the insulin intravenous infusion rate during the last 6–8 h. For patients who could eat, 50% of the total dose was provided as basal insulin and 50% as bolus insulin. To correct premeal hyperglycaemia, a premeal correction dose algorithm, established according to insulin requirements, was implemented, in addition to scheduled bolus insulin doses. Scheduled insulin doses were adjusted according to a prespecified algorithm to achieve a preprandial blood glucose level of 90–130 mg/dl and a postprandial blood glucose level < 180 mg/dl. Throughout hospitalisation, blood glucose levels were recorded at least four times per day, as part of routine clinical care, and seven-point blood glucose monitoring was performed at the beginning and end of hospitalisation and at 3 months. In the control group, these data were collected from measurements previously recorded in the medical records. Treatment at discharge was adjusted according to treatment prior to admission and glycated haemoglobin (HbA_{1c}) levels following an abbreviated treatment algorithm (Figure 1) (12).

Study objectives

The primary objective of the HOSMIDIA study was to evaluate a management protocol for individuals

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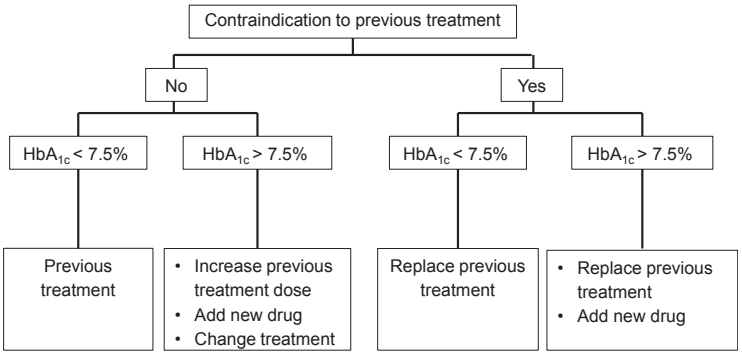

Figure 1 The algorithm used to select treatment at discharge. HbA_{1c}, glycated haemoglobin

with type 2 diabetes during hospitalisation and after discharge in terms of degree of control achieved and complications. To evaluate this objective the following were assessed: glycaemic profiles during hospitalisation and 3 months after discharge; proportion of patients reaching preprandial- and postprandial glucose targets (≤ 130 and ≤ 180 mg/dl, respectively); proportion of patients experiencing hyperglycaemia (> 200 mg/dl); number of documented symptomatic or analytical (< 60 mg/dl) hypoglycaemic episodes during hospitalisation; and the change in HbA_{1c} from baseline to the follow-up visit at month 3. The secondary outcomes included the mean change from baseline to discharge in basal and rapid-acting insulin dose, the length of hospital stay and any adverse events.

Analyses

Quantitative variables were described using measures of central tendency and dispersion (mean, standard deviation, median, minimum and maximum) and qualitative variables were described as absolute and relative frequencies with valid and total percentages. Valid percentages were calculated excluding cases of no data or missing data from the denominator; while total percentages included the total number of patients in that population, even when some did not have data for that variable. For intermediate visits (once per 24 h during hospitalisation), the mean of all visits was calculated for quantitative variables, while for categorical variables the number of patients with the relevant characteristic on at least one visit was calculated. The *t*-test was used to evaluate statistical significance between HbA_{1c} values at baseline and at 3 months. A general linear model was constructed of fasting, mean preprandial and mean postprandial blood glucose values to compare mean values and evaluate the changes between visits (baseline, at discharge and at 3 month follow-up visit).

Results

Baseline characteristics and patient disposition

A total of 141 patients were included in the prospective arm of the study, but seven were excluded as they had no evaluable information. Of the 134 evaluable patients, 97 had all data available during hospitalisation, at discharge and 3-month follow-up visits. Sixty-two patients were retrospectively included in the control group, 23 of whom were treated during hospitalisation with regular human insulin, 17 with neutral protamine Hagedorn (NPH) insulin, eight with premix insulin, seven with long-acting insulin analogues and four with rapid-acting insulin analogues. Demographical and baseline characteristics of the study and control group were comparable, apart from baseline HbA_{1c} level which was higher in the prospective group than in the control group [71.6 ± 22.9 mmol/mol (8.7 ± 2.1%) vs. 62.8 ± 18.6 mmol/mol (7.9 ± 1.7%); $p < 0.05$] (Table 1). In addition, more patients in the control group had been hospitalised owing to cerebrovascular accident (4.5 vs. 14.5%, $p < 0.05$); other reasons for hospitalisation were comparable between both groups.

Glycaemic control

Table 2 shows the mean blood glucose levels during hospitalisation and 3 months after discharge. The mean of all blood glucose measurements during hospitalisation was 167.7 ± 41.1 and 190.5 ± 53.3 mg/dl in the prospective group and control group, respectively. Preprandial mean blood glucose levels (164.2 ± 42.4 and 189.6 ± 52.6 mg/dl for prospective and control arms, respectively; $p < 0.001$), especially prebreakfast (137.0 ± 42.2 and 165.8 ± 56.5 mg/dl; $p < 0.001$), were significantly lower in the prospective group compared with the control group. However, postprandial blood glucose levels were not significantly different between the prospective and control arms (174.4 ± 53.6 and 184.7 ± 85.9 mg/dl,

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Table 1 Demographical and clinical characteristics of patients included in the prospective and control groups

	Prospective group (n = 134)	Control group (n = 62)	p value
Demographical variable			
Age (years), mean ± SD	72.9 ± 10.5	73.7 ± 9.0	0.598
Gender, male/female (%)	54.5/45.5	53.2/46.8	0.870
Weight (kg), mean ± SD	76.3 ± 18.2	77.5 ± 20.0	0.695
BMI (kg/m^2), mean ± SD	29.6 ± 6.8	29.7 ± 6.9	0.897
Duration of diabetes (years), mean ± SD	11.9 ± 9.5	11.7 ± 7.5	0.887
HbA_{1c} (mmol/mol), mean ± SD (%, mean ± SD)	71.6 ± 22.9 (8.7 ± 2.1)	62.8 ± 18.6 (7.9 ± 1.7)	< 0.05
FBG (mg/dl) mean ± SD	189.5 ± 77.5	181.4 ± 79.0	0.511
Reason for hospital admission, n (% valid)			
Cardiovascular disease	34 (25.6)	12 (19.4)	0.342
Cardiovascular disease	8 (6.0)	3 (4.8)	> 0.999
Cerebrovascular accident	6 (4.5)	9 (14.5)	< .05
Infection	48 (36.1)	20 (32.3)	0.601
Surgery	6 (4.5)	2 (3.2)	> 0.999
General medicine	6 (4.5)	5 (8.1)	0.331
Diabetes-related disease	5 (3.8)	1 (1.6)	0.667
Other	20 (15.0)	10 (16.1)	0.844
Antidiabetic treatment on admission, n (%)			
OADs	38 (28.4)	25 (40.3)	0.095
Insulin	120 (89.6)	51 (82.3)	0.155
OADs + insulin*	26 (19.4)	14 (22.6)	–

SD, standard deviation; BMI, body mass index; HbA_{1c}, glycated haemoglobin; FBG, fasting blood glucose; OADs, oral antidiabetic drugs. *Patients also counted in OADs and insulin groups.

Table 2 Mean seven-point blood glucose levels (mg/dl) during hospitalisation and 3 months after discharge in the control and prospective study groups

	Control group	Prospective group		
	During hospitalisation	During hospitalisation	Discharge	3-month follow-up
Prebreakfast	165.8 ± 56.5	137.0 ± 42.2*	121.1 ± 43.6	130.4 ± 47.1
2-h postbreakfast	196.6 ± 90.7	168.5 ± 51.5	153.3 ± 53.4	166.0 ± 53.1
Prelunch	200.2 ± 59.6	163.4 ± 48.7†	147.8 ± 60.5	140.5 ± 53.0
2-h postlunch	236.5 ± 94.7	180.9 ± 62.2	167.8 ± 70.2	169.8 ± 61.4
Predinner	202.5 ± 61.5	192.2 ± 67.2	178.9 ± 73.4	156.3 ± 60.8‡
2-h postdinner	195.3 ± 95.3	178.2 ± 68.8	175.2 ± 72.4	174.0 ± 51.7

*$p < 0.001$ vs. control group; †$p < 0.01$ vs. control group; ‡$p < 0.05$ vs. discharge.

respectively; $p = 0.3$). The mean change in HbA_{1c} from baseline to 3-month follow-up visit was 13.1 mmol/mol (1.2%) [71.6 mmol/mol (8.7%) vs. 58.5 mmol/mol (7.5%)], respectively; $p < 0.05$) (Figure 2).

The mean blood glucose levels obtained from the seven-point profiles in the prospective study group are shown in Figure 3. A significant reduction in mean daily blood glucose levels, as well as pre- and postmeal blood glucose levels, was observed from admission to discharge ($p < 0.01$), and this decrease in blood glucose levels remained at 3 months after discharge. In the prospective study group, the mean pre- and postprandial blood glucose levels decreased from 204.2 ± 68.3 and 217.2 ± 74.6 mg/dl, respectively, at baseline to 149.1 ± 45.1 and 166.1 ± 48.4 mg/dl, respectively, at discharge ($p < 0.01$), and 142.0 ± 45.3 and 171.8 ± 49.0 mg/dl, respectively, at the 3-month follow-up visit ($p < 0.01$). Fasting blood glucose levels (laboratory measurement) also

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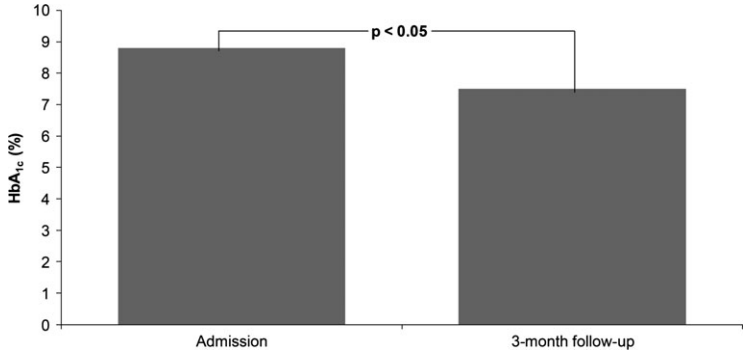

Figure 2 Mean HbA_{1c} levels at admission and at the 3-month follow-up visit in the prospective group.* HbA_{1c}, glycated haemoglobin. *Patients from prospective group with data at baseline and final visit (n = 102)

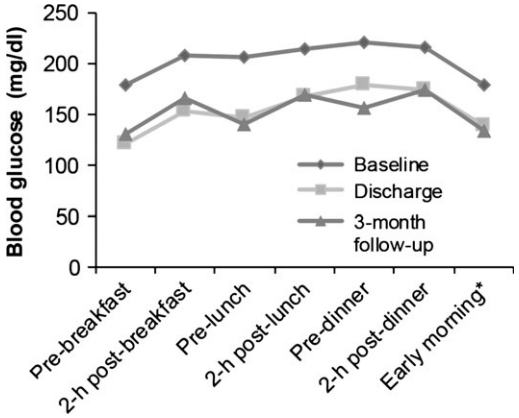

Figure 3 Mean seven-point blood glucose profiles in the prospective study group*. $p < 0.01$ for prelunch blood glucose levels at discharge vs. baseline. $p < 0.01$ for predinner blood glucose levels at discharge vs. baseline. $p < 0.05$ for predinner blood glucose levels at 3-month follow-up visit vs. discharge. *Early morning readings were taken between 03.00 and 04.00

decreased significantly from baseline to discharge (189.5 ± 77.5 vs. 122.1 ± 47.2 mg/dl, respectively; $p < 0.01$), and were maintained at the 3 month follow-up visit (128.9 ± 50.0 mg/dl; $p = 0.454$ vs. discharge).

In the prospective group, 47.7% of patients achieved a fasting blood glucose level between 90 and 130 mg/dl. There was also a significant increase ($p < 0.01$) in people achieving preprandial glycaemic targets; at baseline only 5.7% of patients were achieving a preprandial blood glucose level ≤ 130 mg/dl, but at the time of discharge 48.1% of patients were achieving this target. A similar effect was seen on postprandial glycaemic control, with 30.2% of patients achieving postprandial blood glucose levels ≤ 180 mg/dl at baseline and 46.9% of patients reaching this target at discharge ($p < 0.05$).

Safety

During hospitalisation, 8.8% of patients in the prospective group experienced hyperglycaemia (>200 mg/dl) compared with 19.4% of patients in the control group ($p < 0.05$). There was no significant difference in the number of patients experiencing laboratory (<60 mg/dl) or symptomatic hypoglycaemia in the prospective group compared with the control group (19.3% and 17.7% of patients, respectively, $p = 0.81$).

During the study period, eight adverse reactions were recorded in four patients, none of which were considered related to study medication.

Insulin dose

The mean total subcutaneous dose increased slightly from 45.3 IU/day at baseline to 49.2 IU/day at discharge in the prospective study arm. Both the total basal insulin (from 21.7 to 24.2 IU/day) and total prandial insulin doses (from 20.2 to 24.3 IU/day) increased from baseline to discharge. In the control group, mean total subcutaneous dose was 35.2±22.6 IU/day.

Length of hospital stay

There was no significant difference in the length of hospital stay between the prospective and control arms of the study. The mean length of stay was 8.8 and 10.7 days in the prospective and control arms, respectively.

Treatment modifications at discharge and follow-up

The 97 patients included in the prospective group who had data at admission, discharge and 3 months postdischarge were analysed to assess changes in treatment at discharge and its impact on glycaemic control 3 months after. Treatment was assessed at each of these three points in the study and patients

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were categorised into one of the following groups: diet and/or OADs, basal insulin with or without OADs, or two or more doses of insulin with or without OADs (Figure 4). In comparison with admission, treatment was intensified at discharge in 42% of patients, and the most frequent modification (63.4% of all modifications) was the addition of basal insulin. The treatment given at discharge remained the same up to the 3 month follow-up visit in 89% of patients.

Discussion

This study showed that in the context of clinical practice, protocols to manage hyperglycaemia with a basal–bolus regimen, using insulin glargine and rapid-acting insulin are feasible and enable improved glycaemic control without increasing hypoglycaemic episodes in hospitalised patients with type 2 diabetes. In addition, this study also demonstrated that a simple strategy facilitating the reconciliation of medication on discharge can improve glycaemic control postdischarge.

The consequences of inpatient hypoglycaemia are unclear; however, an observational trial of patients with diabetes hospitalised on a general medicine unit showed that each day with a hypoglycaemic event was associated with a significant increase in length of stay, inpatient death and long-term mortality (18). In addition, multiple studies have shown an association between inpatient hyperglycaemia and poor outcomes (19–25). Although there is no clear evidence for specific blood glucose goals in non-critically ill patients, premeal blood glucose targets < 140 mg/dl with random blood glucose < 180 mg/dl are considered reasonable, provided these targets can be safely achieved.

In this study, the use of a basal–bolus regimen resulted in a significant reduction in blood glucose levels from admission to discharge, highlighting that the use of insulin in this manner enables rapid glycaemic control. This improvement in glycaemic control meant that a greater number of patients reached glycaemic targets, with fewer experiencing hyperglycaemia compared with the control group, without a significant increase in the number of patients experiencing hypoglycaemia including severe hypoglycaemia. This confirmed that scheduled subcutaneous insulin with basal, nutritional and correction components is an adequate method for achieving and maintaining glucose control in non-critically ill hospitalised patients, and extends our knowledge as it was performed during regular clinical practice.

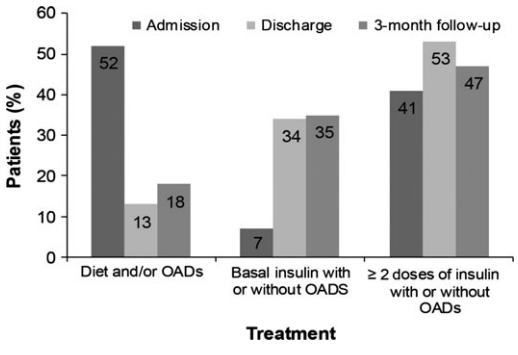

Figure 4 The evolution of diabetes treatment from admission to 3-months follow-up in the prospective study group. OAD, oral antidiabetic drug

These results are consistent with previous randomised studies. The RABBIT-2 trial in non-critically ill, hospitalised patients with type 2 diabetes found that a basal–bolus regimen with insulins glargine and glulisine was safe and effective compared with sliding scale insulin (SSI) (15). A significant difference in mean blood glucose during hospitalisation was seen between the basal–bolus and SSI groups (166 ± 32 vs. 193 ± 54 mg/dl, respectively; $p < 0.001$). The RABBIT-2 Surgery trial extended these results, demonstrating that a basal–bolus insulin regimen improved glycaemic control and reduced complications in general surgery patients (14). The Basal Plus trial compared a third regimen involving once-daily insulin glargine with correctional doses of insulin glulisine before meals (basal-plus regimen) with a full basal–bolus regimen or SSI (13). This study found that treatment with the basal-plus regimen was as effective as the basal–bolus regimen, and that both significantly reduced mean daily blood glucose compared with SSI ($p = 0.04$). Another study by Umpierrez et al. compared the use of a basal–bolus regimen, involving insulins detemir and aspart, with a split-mixed regimen involving NPH and regular human insulin (17). This trial found that there was no difference in glycaemic control or frequency of hypoglycaemia between the two different insulin regimens.

The seven-point blood glucose profile during hospitalisation showed higher preprandial mean blood glucose levels before lunch and dinner compared with breakfast. This may reflect more aggressive titration of basal insulin; however, this seems unlikely as the increase in basal insulin dose during hospitalisation was small and similar to that of prandial insulin. Other factors that might be involved include carbohydrate distribution and glucocorticoid treatment. The study protocol included only three meals, but 52% of patients consumed snacks, mainly in the afternoon. This represented 13.7% of mean daily carbohydrate intake at admission and 12.4% at

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discharge and could justify the higher blood glucose level before dinner. In addition, 27% of the patients in the prospective arm and 24.2% in the control group received glucocorticoid during hospitalisation, most with intermediate-acting glucocorticoid, which induced hyperglycaemia predominantly in the evening (26,27).

The transition of diabetes care at discharge receives little attention and previous studies have demonstrated that this is an area of unmet need (28). A retrospective study of 24,953 older people with diabetes hospitalised following acute myocardial infarction found that over 10% have their diabetes medication discontinued at the time of discharge (29). A second retrospective study of 1359 older people with diabetes and HbA_{1c} 63.9 mmol/mol (8%) at admission found that fewer than 25% had their diabetes medication regimen altered at discharge, and that 32% had no change in medication at discharge and no timely follow-up (30). The findings of the study reported here are, therefore, important as they demonstrate that a simple algorithm can be used to select the treatment at discharge and improve post-discharge glycaemic control.

The most frequent modification of treatment in this study was the addition of basal insulin (63.4% of all modification). This was also observed in a previous study, which found that people with uncontrolled diabetes who had not been previously treated with insulin experienced significantly improved glycaemic control at 1-year follow-up if they were discharged on insulin therapy rather than standard care (31). Moreover, hospital admission can be a useful time to modify therapy and improve long-term glycaemic control in people with diabetes, particularly in the subgroup of patients requiring treatment intensification to insulin therapy, as hospitalisation may help overcome barriers to insulin initiation. Finally, the persistence at 3 months of the treatment given at discharge in 89% of patients reinforces the effectiveness of this simple strategy.

This study also expands our knowledge of the use of basal–bolus insulin in non-critically ill hospitalised patients as it was performed during regular clinical practice, rather than as part of a multicenter randomised trial. Consequently, the study demonstrates that the use of basal–bolus regimens is effective when implemented in clinical practice, as well as highlighting the value of an algorithm to guide treatment at discharge to ensure that glycaemic control is maintained in the outpatient setting. This must, however, be considered in the light of the limitations of the study. It was not a randomised trial, instead incorporating a retrospective control group and a prospective group, both performed as part of routine clinical practice, comparing the new dosing algorithm during hospitalisation with historical data. Furthermore, although the improved glycaemic control did not significantly decrease the length of hospital stay, there was a trend towards a shorter hospital stay in the prospective group. This might have been because of the low patient numbers in this study and the variety of different reasons for hospitalisation.

In conclusion, this study confirms that protocols to safely manage hyperglycaemia with a basal–bolus insulin regimen with insulin glargine as the basal insulin are feasible in clinical practice and improve glycaemic control without increasing hypoglycaemic episodes in hospitalised patients with type 2 diabetes. In addition, the results emphasise that hospitalisation can be an important time for improving glycaemic control postdischarge in patients with uncontrolled diabetes prior to hospital admission, and demonstrate that this improvement can be achieved by applying a simple treatment algorithm to facilitate medication reconciliation at discharge. Even though this study adds to our knowledge of this period of transition in care, further studies are needed to develop strategies to improve the discharge process in patients with diabetes, with the overall goal of improving quality of care and reducing unnecessary readmissions.

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