Temporal patterns of hypoglycaemia and burden of sulphonylurea related hypoglycaemia in UK hospitals: a retrospective multi-centre audit of hospitalised patients with diabetes

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Temporal patterns of hypoglycaemia and burden of sulphonylurea related hypoglycaemia in UK hospitals: a retrospective multi-centre audit of hospitalised patients with diabetes

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Abstract:

Objectives: To determine whether temporal patterns of hypoglycaemia exist in inpatients with diabetes 'at risk' of hypoglycaemia (those on insulin and/or sulphonylureas), and if so whether patterns differ between hospitals and between these treatments.

Setting: Retrospective multicentre audit of inpatients with diabetes involving 11 acute UK NHS Trusts.

Participants: Capillary blood glucose readings of 3.9mmol/l or less (hypoglycaemia) for all inpatients with diabetes 'at risk' of hypoglycaemia were extracted from Abbott Precision Web Point-of-Care Data Management System™ over a four-week period. Overall 2,521 readings of 3.9mmol/l or less (hypoglycaemia) occurring in 866 subjects between 01/06/2013 and 29/06/2013 were analysed.

Interventions: Not applicable

Primary and secondary outcome measures: Not applicable

Results: The majority (65%) occurred between 21:00-08:59 hours, a pattern common to all Trusts. This was more frequent in sulphonylurea than insulin treated subjects (75.3% vs 59.3%, p=0.0001). Furthermore, hypoglycaemic readings were more frequent between 05:00-07:59 hours in sulphonylurea than insulin treated subjects (46.7% vs 22.7% of readings for respective treatments, p=0.0001). Sulphonylureas accounted for 31.8% of all hypoglycaemic readings. As a group, sulphonylurea treated subjects were older (median age 78 vs 73 years, p=0.0001) and had lower HbA1c [median 56mmol/mol (7.3%) vs 69mmol/mol (8.5%), p=0.0001]. Hypoglycaemic readings per subject were as frequent for sulphonylurea as for insulin treated subjects (median=2 for both) as were the proportion in each group with ≥5 readings (17.3% vs 17.7%).

Conclusions: In all Trusts hypoglycaemic readings were more frequent between 21:00-08:59 hours in 'at risk' inpatients with diabetes, with a greater frequency in the early morning period (05:00-07:59 hours) in sulphonylurea treated inpatients. This may have implications for the continuing use of sulphonylureas in the inpatient setting.

Trial registration: Not applicable.

Article summary:

Strengths and limitations of this study:

1. This study reports the burden of sulphonylurea related inpatient hypoglycaemia in NHS Trusts which has not been previously documented.
2. This study reports that the risk of hypoglycaemia appears to be greater in sulphonylurea treated inpatients than insulin treated inpatients in early morning hours.
3. This study confirms a previous single centre report that hypoglycaemia occurs more commonly at night-time/early morning in NHS Trusts participating in this study.
4. One of the limitations of this study was the inability to obtain the total number of inpatients with diabetes, type of diabetes and proportion of inpatients treated with insulin and sulphonylureas who did not experience hypoglycaemia.
5. Another limitation was that the detection of hypoglycaemic readings was strongly influenced by glucose monitoring frequency which was pre-determined.

Introduction:

Until recently tight glycaemic control in inpatients has been considered to be important in reducing morbidity and mortality as previous studies have shown that inpatient hyperglycaemia is associated with poorer outcomes (1, 2). However its advantages are offset by the risk of hypoglycaemia. Although the available data does not conclusively suggest that inpatient hypoglycaemia is an independent risk factor for mortality per se, there is increasing evidence that it is associated with increased mortality, morbidity and length of stay (3-5). In the NICE-SUGAR multinational randomised control trial severe hypoglycaemia was thirteen times more frequent in the intensively treated group (6.8% vs 0.5%, $p<0.001$) in which there was found to be a significantly higher ninety-day mortality compared to the conventional group (6). Subsequently, a meta-analysis that included the NICE-SUGAR data concluded that tight glycaemic control (with insulin therapy) increased the risk of hypoglycaemia with no overall mortality benefit (7). Indeed, some have suggested that hypoglycaemia should now be considered a new factor for cardiovascular risk (8).

The burden of inpatient hypoglycaemia in NHS hospitals has been well highlighted by the annual National Diabetes Inpatient Audit (NaDIA), the largest one week snapshot audit covering >95% of all acute NHS Trusts in England and Wales. In 2012, NaDIA reported that in England alone, 22.4% of inpatients experienced at least one hypoglycaemic episode [capillary blood glucose (CBG) ≤3.9mmol/l] and 2.2% had at least one hypoglycaemic episode that required rescue injectable therapy (9). Hypoglycaemia was significantly higher in those on insulin therapy; 45.3% of patients with type 1 diabetes and 31.8% of patients with type 2 diabetes treated with insulin had at least one episode of hypoglycaemia (9).

The American Diabetes Association (ADA) recommendation that insulin therapy in the form of a basal bolus regimen should be used as the preferred method of achieving and maintaining glycaemic control for all inpatients with diabetes has been widely adopted in the US (10). In the UK, there is no national consensus on the type of therapy that should be used for managing inpatients with diabetes who had not previously been on insulin i.e. whether oral agents be continued or there be a temporary switch to insulin therapy. Reluctance to adopt the ADA recommendation is supported by the frequency of drug errors and hypoglycaemia associated with insulin use from NaDIA data (9). However, to date, the extent of inpatient hypoglycaemia in the UK from the use of oral agents that can precipitate hypoglycaemia, namely sulphonylurea therapy is unknown.

In a recent study of inpatient hypoglycaemia in one NHS hospital, we found that more than two-thirds of all hypoglycaemic readings occurred between 21:00-08:59 hours (11). The current study was designed to determine whether similar or other temporal patterns of hypoglycaemia exist in other NHS hospitals and if so, to consider the possible reasons for any observed differences and potential preventative strategies. Additionally, in the previous study there appeared to be more hypoglycaemic readings in those on sulphonylurea therapy than anticipated, but that study was not specifically designed to examine this (11). As a result of this anecdotal observation and in view of the ADA's abandonment of sulphonylurea therapy in the inpatient setting, the current study was also designed to compare hypoglycaemic rates and patterns in sulphonylurea and insulin treated inpatients.

Methods:

The Joint British Diabetes Society (JBDS) recommends all adults with blood glucose ≤3.9mmol/l in hospitals be treated whether or not they are symptomatic (12). We therefore defined hypoglycaemia in our inpatient cohort as CBG ≤3.9mmol/l irrespective of the presence or absence of symptoms. Severe hypoglycaemia is usually defined as an episode of hypoglycaemia requiring third party assistance. This definition is not applicable to inpatients as most patients will not have direct access to carbohydrates and therefore require third party assistance from a health care professional even if the event was mild. We therefore used NaDIA 2012's biochemical classification of hypoglycaemia in which mild hypoglycaemia is defined as a CBG 3-3.9mmol/l and severe hypoglycaemia as a CBG ≤2.9mmol/l, irrespective of symptoms and necessity for third party assistance (9). Although not strictly correct, for the purpose of this study, we defined night-time hypoglycaemia as that between 21:00-08:59 hours and daytime hypoglycaemia as that between 09:00-20:59 hours.

The study was a four week retrospective multi-centre audit, undertaken between 01/06/13 and 29/06/13 in 11 NHS Trusts. Institutional approval was obtained from the audit department of each individual NHS Trust. All Trusts used Precision Xceed Pro™ as the only CBG monitoring system across the entire hospital. All CBG readings were relayed remotely to Precision Web Point-of-Care Data Management System™ (Abbott Diabetes Care Inc., Alameda, CA 94502, USA). From this database, all CBG readings of ≤3.9mmol/l were extracted at each NHS site including patients' unique identifiers, ward location, date and time of measurement. Each CBG reading of ≤3.9mmol/l was considered as an episode but

recurrent readings of ≤3.9mmol/l within 2 hours of a previously documented hypoglycaemic episode were automatically excluded as they could reflect re-testing for the same event.

We included adult (≥18 years) inpatients with diabetes 'at risk' of hypoglycaemia i.e. those treated with insulin and/or sulphonylureas. Data from Accident and Emergency departments, paediatric and day case areas were excluded. Age, length of stay until 15/07/13, type of therapy and HbA1c (within the preceding 3 months) data were collected. Hospital bed numbers (excluding maternity and the previously mentioned areas) and factors that could influence institutional hypoglycaemia rates such as average weekly hours spent by diabetes specialist staff on inpatient diabetes care, meal timings, bedtime snack availability and frequency of CBG monitoring were obtained.

Statistics:

After completion of data collection, unique patient identifiers were removed and results were analysed using Microsoft Excel 2007, GraphPad and IBM SPSS Statistics v20. Descriptive statistics were used to evaluate characteristics of study subjects. Unpaired t test was used to compare means in parametric continuous data and Wilcoxon-Mann-Whitney test to compare non-parametric continuous data. Fisher's exact test was used to compare categorical data. Pearson correlation was used to evaluate linear correlation. All p values are two tailed and <0.05 was considered statistically significant.

Results:

Overall, 2,521 hypoglycaemic readings in 866 subjects from 11 NHS Trusts were analysed (Tables 1 and 2). Hypoglycaemia was exclusively attributable to sulphonylureas in 32.7% of all subjects who had recorded hypoglycaemia and accounted for 31.8% of all hypoglycaemic readings. In subjects exclusively treated with sulphonylurea therapy, 22.5% of readings were severe as opposed to 35.9% in insulin treated subjects. There was no difference in the percentage of subjects experiencing ≥5 hypoglycaemic readings between those treated with sulphonylureas and those on insulin therapy (17.3% vs 17.7%, p=0.923). Additionally, the number of hypoglycaemic readings per subject was the same for sulphonylurea and insulin treated subjects (median= 2 for both, p=0.888). Length of stay was similar between the two groups (median 11 vs 10 days, p=0.098). Subjects on sulphonylureas were significantly older (median age 78 vs 73 years, p=0.0001) and had lower HbA1c [median 56mmol/mol (7.3%) vs 69mmol/mol (8.5%), p=0.0001]. Length of stay correlated significantly with the number

of hypoglycaemic readings per subject for both insulin (r=0.286, p=0.0001) and sulphonylurea (r=0.167, p=0.005) treated subjects but did not correlate with age and HbA1c.

Temporal pattern analysis showed that hypoglycaemic readings were most frequent between 05:00-07:59 hours. Not surprisingly, the other frequent times coincided with glucose monitoring times i.e. before lunch, evening meal and bedtime. Interestingly, a significant number of hypoglycaemic readings occurred between 02:00-02:59 hours in all Trusts (even though routine 3am glucose monitoring was performed only by Trust 2). The observed patterns were similar in all Trusts (Figure 1). The relative frequency of hypoglycaemic readings between 05:00-07:59 hours in sulphonylurea treated subjects was twice that of the insulin treated subjects (46.7% vs 22.7%, p=0.0001), despite similar glucose monitoring frequency for both therapies (Figure 2). Overall, 65% of all hypoglycaemic readings occurred at night-time, ranging from 54.1% to 72.2% across the 11 Trusts. This was significantly greater in sulphonylurea compared to insulin treated subjects (75.3% vs 59.3%, p=0.0001). There was a positive correlation between proportion of night-time to daytime hypoglycaemic readings and proportion of hypoglycaemic readings attributable to sulphonylureas for each Trust (r=0.787, p=0.004). There was no significant difference in the number of hypoglycaemic readings per day between weekdays and weekends [mean (SD) 88.15±16.95 vs 84.22±12.16, p=0.538]. There was no relationship between the time reported to be spent by diabetes specialist nurses on inpatient care and hypoglycaemic readings per 100 bed ratio (r=-0.342, p=0.303).

Discussion:

Having expected to find variations in temporal patterns of hypoglycaemic readings related to differing clinical practices we found that all Trusts demonstrated the same pattern of hypoglycaemia as seen in the index hospital (11). We had previously postulated that prolonged fasting (14 hours) between evening meal and breakfast as well as the lack of bedtime carbohydrate snacks in the index hospital as important contributory factors. It is therefore of interest that all Trusts in this study reported similar prolonged fasting (13.5-15.5 hours) after the evening meal and that none guaranteed the provision of bedtime carbohydrate snacks. This feeding practice appears to be common in UK hospitals as reported in our previous online survey of NHS Trusts (11). We believe that addressing these meal timings and provision of bedtime carbohydrate snacks could reduce the frequency of hypoglycaemia in UK hospitals.

The second important finding was the extent of inpatient hypoglycaemia related to the use of sulphonylurea therapy. Whilst the burden of sulphonylurea related hypoglycaemia needing emergency medical assistance is increasingly recognised in the community setting (13-15), its contribution to inpatient hypoglycaemia appears not to have been fully appreciated. In this study we found that one third of hypoglycaemic readings were related to sulphonylurea therapy and indeed the frequency of inpatients experiencing markedly recurrent hypoglycaemia (≥5 hypoglycaemic readings) was the same as those receiving insulin. In a recent single centre report from one of the few US hospitals where oral agents continue to be used in the management of inpatient diabetes, one in five patients treated with sulphonylureas experienced at least one hypoglycaemic episode during their inpatient stay (16). In our study it was not possible to determine this as the initial source data was hypoglycaemic readings recorded in the Precision Web Point-of-Care Data Management System™ and therefore the total number of inpatients with diabetes was not known.

There are a number of factors that may contribute to frequent hypoglycaemia in inpatients on sulphonylurea therapy. Health care professionals have greater concern for insulin treated inpatients than those on tablets who are often considered to have less severe diabetes and therefore perceived less likely to suffer hypoglycaemia. Physicians, nurses and even the small subgroup of patients who self-manage their diabetes in hospital are less inclined to adjust doses of oral hypoglycaemic agents than insulin even during periods of varying meal intake. This is reflected in the TOPDOC study of UK trainee-doctors, who when given an example of a patient with poor control, were less likely to alter the dose of oral agents compared to insulin (65% vs 79%) (17). Finally, the pharmacokinetic profile of sulphonylureas are less predictable compared to insulin especially in the complex inpatient setting with changing nutritional status, renal function etc.

In the US, insulin therapy is the preferred treatment for all inpatients with diabetes (10). The basal-bolus system, utilising well tested insulin regimens such as the RABBIT medical and surgical protocols are extensively used and have been shown to be associated with low frequencies of inpatient hypoglycaemia (18, 19). It is unlikely that such regimens will be adopted in the UK in the near future as this would require transferring up to one in six inpatients with diabetes to basal-bolus insulin therapy, when at present the expertise for initiating and monitoring inpatients on insulin therapy is very limited. Thus, NaDIA 2012

found that 32.2% of NHS England Trusts did not have a dedicated diabetes inpatient specialist nurse (9). Secondly, very serious concerns have been raised on the safe use of insulin in inpatients in UK (20-22). The National Patient Safety Agency identified 16,600 reported incidents involving insulin between November 2003 and November 2009, the majority occurring in inpatients; 24% caused harm to the patient and there were 18 individual incidences associated with fatal or severe outcomes (22). Importantly these figures represent the tip of the iceberg as it is recognised that such errors are grossly under-reported in the UK. Thus, in contrast, NaDIA 2012 found that in England 21.8% of inpatients with diabetes treated with insulin therapy in the week of the audit had one or more insulin errors, summating to one hundred and fifty thousand errors each year (9). Furthermore, in a recent retrospective survey of diabetes inpatient teams at least twelve episodes of serious harm related to inpatient hypoglycaemia (including death, cardiac arrest and irreversible brain injury) were reported to have occurred in the 41 UK Trusts who participated in the survey covering a twelve month period. Insulin therapy was implicated in at least ten of these events (in press). It is hoped that in the future electronic prescribing and clinical decision support systems will help to minimise these errors while recognising that such systems are not infallible and will not prevent errors in insulin administration nor in management decisions (23, 24).

Finally, one of the aims of this multi-site study was to identify and learn from differences between Trusts. Trust 2 had the lowest frequency of both mild and severe hypoglycaemia per 100 beds and the lowest number of recurrent hypoglycaemic readings. It may be relevant that this Trust introduced a number of changes in practice to reduce their institutional hypoglycaemia rates following a fatal adverse event related to inpatient hypoglycaemia. These included intentionally relaxing inpatient glycaemic targets to 7-11mmol/l in comparison with the currently recommended acceptable range of 4-12mmol/l (25), introducing an aggressive capillary glucose monitoring regimen including 3am glucose testing (the only trust to do so) and implementing intensive education programs for nursing and medical staff achieved by increasing the number of inpatient diabetes specialist nurses and their time devoted to inpatient care (Table 1). Whether replicating these practices in other Trusts would lead to reductions in their institutional hypoglycaemia rates can only be speculated.

We recognise several limitations to our study. The source data was the Precision Web Point-of-Care Data Management System™; as a result we were unable to obtain the total number of inpatients with diabetes, a breakdown by type of diabetes, and the proportions treated with insulin and sulphonylureas who did not experience hypoglycaemia. Therefore, we were unable to calculate the exact risk with each therapy per se. The detection of hypoglycaemic readings was strongly influenced by glucose monitoring frequency which was pre-determined and similar in all hospitals; occurring at meal times and bedtime. Continuous glucose monitoring would almost certainly reveal an even greater frequency of hypoglycaemic readings, especially at night-time when patients are not routinely monitored. As previously mentioned while hospital meal times may be a major contributory factor for the frequency of night-time and early morning hypoglycaemia, we acknowledge that we did not consider other important factors for hypoglycaemia in hospitalised patients such as sepsis, renal and liver disease, overall nutritional status and changing drug therapies such as tapering of steroid therapy. Despite these limitations we believe that this study provides important information on institutional patterns of inpatient hypoglycaemia in the 'at risk' inpatients and the impact of sulphonylurea therapies.

In summary in UK hospitals, hypoglycaemia is detected more frequently during the period between 21:00-08:59 hours (night-time), and sulphonylurea therapy appears to present a greater risk than insulin particularly between 05:00-07:59 hours (early morning). Institutional feeding patterns appear to be contributory but further work is required to determine whether a change in meal times would reduce institutional hypoglycaemia rates. Importantly, our findings may have implications for the continued use of sulphonylureas in the UK in the inpatient setting.

What is already known on this topic?

A single NHS Trust previously reported that hypoglycaemia was more frequent at night-time in hospitalised patients.

It was not known whether this pattern was common in other NHS Trusts.

The burden of inpatient hypoglycaemia due to sulphonylurea therapy was not previously known in NHS Trusts.

What this study adds:

Hypoglycaemia is detected more commonly at night-time/early morning in all participating NHS Trusts.

Similar problems with institutional feeding patterns exist in all participating NHS Trusts.

There is a substantial burden of sulphonylurea related inpatient hypoglycaemia and it appears to present a greater risk than insulin therapy in early morning hours.

These observations should lead to a review of feeding times and the use of sulphonylureas in hospitalised patients.

Figure legends:

Figure 1: Temporal patterns of hypoglycaemic readings over the 24 hour period in the individual 11 NHS Trusts. The x axis represent the time period, for e.g. 0 represents the time period between 00:00 and 00:59 hours, 1 represents the time period between 01:00 and 01:59 hours etc. The y axis represents the number of hypoglycaemic readings occurring in that time period. The figure demonstrates very similar temporal patterns for all Trusts.

Figure 2: Temporal patterns of hypoglycaemic readings over the 24 hour period in all subjects on insulin, sulphonylureas and both. The x axis represent the time period, for e.g. 0 represents the time period between 00:00 and 00:59 hours, 1 represents the time period between 01:00 and 01:59 hours etc. The y axis represents the number of hypoglycaemic readings occurring in that time period. The figure demonstrates that the highest frequency occurs between 05:00 to 07:59 hours for both insulin and sulphonylurea therapies. .

Table 1: Table represents individual data from the 11 NHS Trusts.

Table 2: Table shows combined data from all Trusts for subjects on insulin, sulphonylureas or both forms of therapy.

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Declaration of competing interests:

All three authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: the MaGIC study group meetings were sponsored by Abbott, UK who also assisted in extraction of data from Precision Web Point-of-Care Data Management System™ but was not involved in the design or origin of the study, nor in funding or influencing the analysis, nor in interpretation or reporting of the data nor in the preparation of this manuscript; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Transparency declaration statement:

The lead author RR (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data sharing statement:

Additional data is available by emailing the corresponding author Dr Gerry Rayman-gerry.rayman@ipswichhospital.nhs.uk

Contributorship and authorship statement:

RR designed data collection tools, monitored data collection, cleaned and analysed the data, drafted and revised the paper. He is the guarantor. CK assisted in data collection and revised the draft paper. GR initiated the audit, monitored data collection, drafted and revised the paper and was the lead for the audit. All other members of MaGIC study group designed the audit, assisted in data collection and revised the draft paper. The following are members of the MaGIC (Managing Glycaemia using Innovations in Care) study group (UK): Gerry Rayman (Group lead, The Ipswich Hospital NHS Trust), Rajesh Rajendran (The Ipswich Hospital NHS Trust), Chris Kerry (The Ipswich Hospital NHS Trust), Ainslie Lang (Royal

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Table 1:

Variable		Each individual Trust data											Combined data across all Trusts
		1	2	3	4	5	6	7	8	9	10	11	
Number of beds*		537	690	344	264	449	939	680	997	274	690	293	6157
Diabetes Inpatient Specialist Nurse time devoted to inpatient diabetes care†		75.5	97	30	20	20	78	75	52	10	32	48.5	538
Number of 'at risk' subjects	All	85	82	40	43	67	156	73	155	50	74	41	866
	Insulin	50	56	26	18	39	103	44	96	29	52	28	541
	Sulphonylurea	32	25	12	22	24	44	22	52	18	20	12	283
	Both‡	3	1	2	3	4	9	7	7	3	2	1	42
Number of hypoglycaemic readings	All	334	163	136	115	264	432	234	316	159	198	170	2521
	Insulin	219	107	90	61	161	257	161	199	96	118	125	1594
	Sulphonylurea	105	55	34	51	89	154	61	104	46	68	34	801
	Both‡	10	1	12	3	14	21	12	13	17	12	11	126
	Mild hypoglycaemia	239	124	86	81	177	309	165	203	103	134	108	1729
	Severe hypoglycaemia	95	39	50	34	87	123	69	113	56	64	62	792
Hypoglycaemia per 100 bed ratio§	All	62.2	23.6	39.5	43.6	58.8	46	34.4	31.7	58	28.7	58	41
	Mild hypoglycaemia	44.5	18	25	30.7	39.4	32.9	24.3	20.4	37.6	19.4	36.9	28.1
	Severe hypoglycaemia	17.7	5.6	14.5	12.9	19.4	13.1	10.1	11.3	20.4	9.3	21.1	12.9
Hypoglycaemic readings per subject	Median	2	1	2	2	3	2	2	2	2	1	2	2
	Mean	3.93	1.99	3.4	2.7	3.94	2.77	3.21	2.04	3.18	2.68	4.15	2.91
	Range	1-29	1-9	1-11	1-23	1-18	1-16	1-13	1-11	1-12	1-14	1-30	1-30
Subjects with ≥5 readings of hypoglycaemia during the study period		20	7	10	5	18	27	15	15	11	15	11	154
Frequency of glucose monitoring	Insulin	BD-QDS	QDS and 3am	QDS	QDS	BD-QDS	QDS	QDS	QDS	QDS	QDS	QDS	-
	Sulphonylurea	BD-QDS	QDS and 3am	BD-QDS	BD	BD-QDS	BD-QDS	QDS	BD-QDS	QDS	OD-QDS	QDS	-
Hospital meal timings	Breakfast	7:30	7:00	7:00 - 8:00	8:30	7:30 - 8:30	7:00 - 9:00	7:30 - 8:30	7:45 - 8:30	7:45 - 8:30	7:00 - 8:00	8:00	-
	Afternoon meal	12:00	12:00	12:00-13:00	12:15	12:00-13:00	12:00-14:00	11:30-12:45	12:00-13:00	12:00-13:00	12:00-13:00	12:00	-
	Evening meal	17:00	17:00	18:00-19:00	17:00	17:00-18:00	17:00-19:00	16:30-17:45	17:00-18:00	17:00-18:00	17:00-18:00	17:00	-
Time period of hypoglycaemic readings													
Daytime	09:00-14:59	75	30	25	8	33	61	45	46	25	14	31	393
	15:00-20:59	50	33	29	25	51	78	46	65	24	41	47	489
	09:00-20:59	125	63	54	33	84	139	91	111	49	55	78	882
Night-time	21:00-02:59	93	36	36	34	69	133	68	76	45	51	45	686
	03:00-08:59	116	64	46	48	111	160	75	129	65	92	47	953
	21:00-08:59	209	100	82	82	180	293	143	205	110	143	92	1639
Percentage of night-time hypoglycaemia		62.6	61.3	60.3	71.3	68.2	67.8	61.1	64.9	69.2	72.2	54.1	65

*Bed numbers exclude paediatric, maternity and day case units

†Average Diabetes Inpatient Specialist Nurse time (hours per week) devoted to inpatient diabetes care

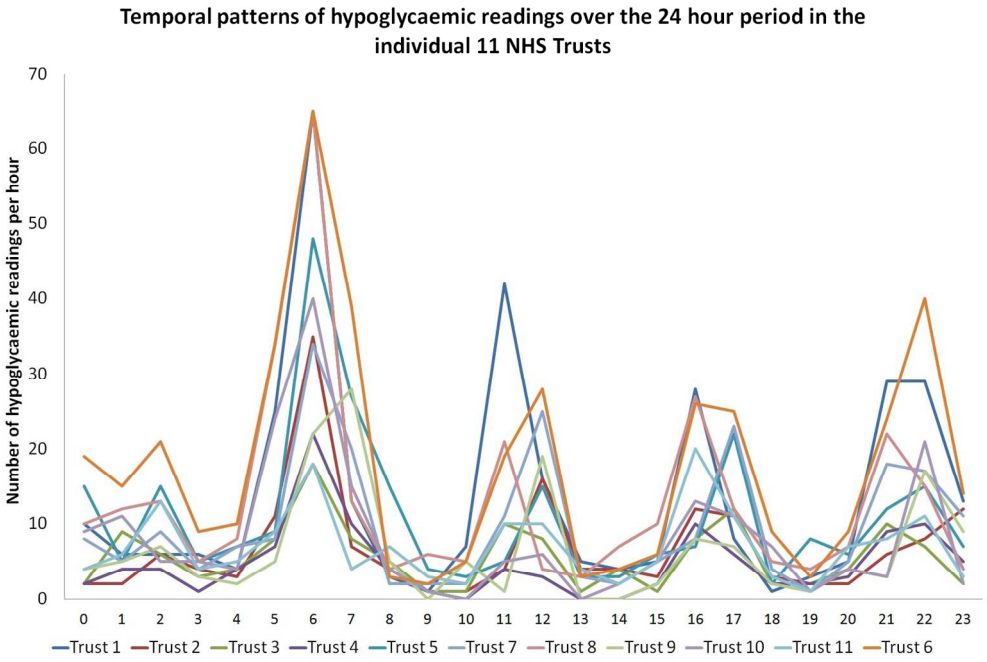
‡Subjects on both insulin and sulphonylurea therapy

§Calculated as 100 * number of hypoglycaemic readings ÷ number of beds

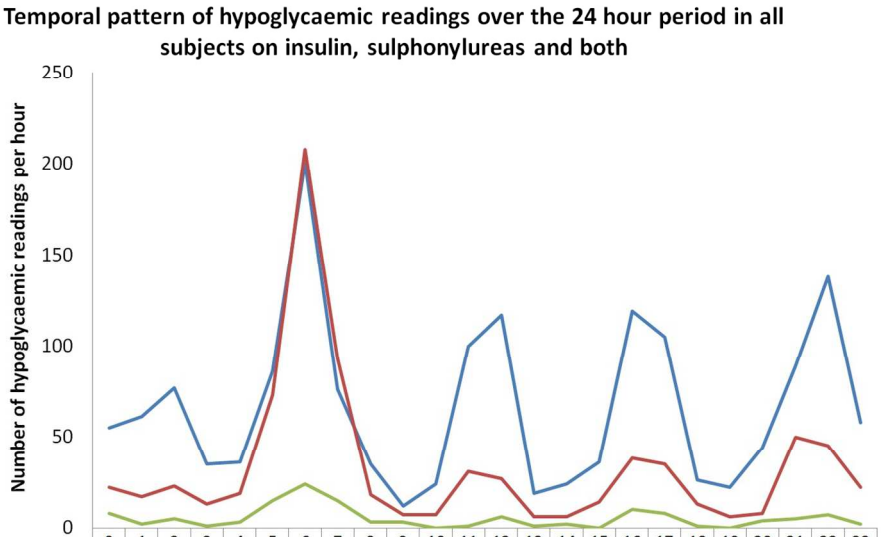
No Trust guaranteed the provision of a bedtime snack for inpatients with diabetes

Table 2:

Variable		All	Insulin	Sulphonylurea	Both Insulin and Sulphonylureas
Number of subjects		866	541	283	42
Number of hypoglycaemic readings (%)	All	2521	1594	801	126
	Severe hypoglycaemia	792 (31.4)	572 (35.9)	180 (22.5)	40 (31.7)
	Mild hypoglycaemia	1729 (68.6)	1022 (64.1)	621 (77.5)	86 (68.3)
Subjects with ≥5 readings of hypoglycaemia per subject during the study period (%)		154 (17.8)	96 (17.7)	49 (17.3)	9 (21.4)
			p=0.923		
Number of hypoglycaemic readings per subject	Mean±SD (Range)	2.91±3.16 (1-30)	2.95±3.29 (1-30)	2.83±2.89 (1-29)	3±3.21 (1-12)
	Median (Interquartile range)	2 (1-3)	2 (1-3)	2 (1-4)	1 (1-3.25)
			p=0.888		
Age (years)	Mean±SD (Range)	71±16 (18-98)	67±18 (18-97)	76±10 (42-98)	75±9 (46-91)
	Median (Interquartile range)	75 (64-82)	73 (56-81)	78 (70-83)	77 (69-81)
			p=0.0001		
HbA1c in mmol/mol (%)	Mean [Range]	n=575*	n=364*	n=181*	n=30*
		69(8.5) [28(4.7)-177(18.3)]	73(8.8) [28(4.7)-177(18.3)]	60(7.6) [33(5.2)-161(16.9)]	73(8.8) [46(6.4)-115(12.7)]
	Median [Interquartile range]	64(8) [53(7)-80(9.5)]	69(8.5) [56(7.3)-83(9.7)]	56(7.3) (47(6.5)-66(8.2)]	73(8.8) [55(7.2)-86(10)]
			p=0.0001		
Length of stay (days)	Mean±SD (Range)	n=862*	n=540*	n=282*	n=40*
		17±17.1 (1-101)	16.1±17 (1-101)	17±16.2 (1-100)	25±21.9 (1-82)
	Median (Interquartile range)	11 (5-22)	10 (4-21)	11 (6-23)	20 (7-45)
			p=0.098		
Temporal pattern of hypoglycaemic readings					
Daytime hypoglycaemia	09:00-14:59	393	296	84	13
	15:00-20:59	489	352	114	23
	Total 09:00-20:59	882	648	198	36
Night-time hypoglycaemia (%)	21:00-02:59	686	478	179	29
	03:00-08:59	953	468	424	61
	Total 21:00-08:59	1639 (65)	946 (59.3)	603 (75.3)	90 (71.4)
			p=0.0001		
*Subjects in whom data available					



Temporal patterns of hypoglycaemic readings over the 24 hour period in the individual 11 NHS Trusts. The x axis represent the time period, for e.g. 0 represents the time period between 00:00 and 00:59 hours, 1 represents the time period between 01:00 and 01:59 hours etc. The y axis represents the number of hypoglycaemic readings occurring in that time period. The figure demonstrates very similar temporal patterns for all Trusts.
446x300mm (96 x 96 DPI)



	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Insulin (N=1594)	55	61	77	35	36	86	200	76	35	12	24	100	117	19	24	36	119	105	26	22	44	89	138	58
Sulphonylurea (N=801)	22	17	23	13	19	73	208	93	18	7	7	31	27	6	6	14	38	35	13	6	8	50	45	22
Both (N=126)	8	2	5	1	3	15	24	15	3	3	0	1	6	1	2	0	10	8	1	0	4	5	7	2

Temporal patterns of hypoglycaemic readings over the 24 hour period in all subjects on insulin, sulphonylureas and both. The x axis represent the time period, for e.g. 0 represents the time period between 00:00 and 00:59 hours, 1 represents the time period between 01:00 and 01:59 hours etc. The y axis represents the number of hypoglycaemic readings occurring in that time period. The figure demonstrates that the highest frequency occurs between 05:00 to 07:59 hours for both insulin and sulphonylurea therapies.
398x259mm (96 x 96 DPI)

BMJ Open

Temporal patterns of hypoglycaemia and burden of sulphonylurea related hypoglycaemia in UK hospitals: a retrospective multi-centre audit of hospitalised patients with diabetes

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Temporal patterns of hypoglycaemia and burden of sulphonylurea related hypoglycaemia in UK hospitals: a retrospective multi-centre audit of hospitalised patients with diabetes

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Abstract:

Objectives: To determine whether temporal patterns of hypoglycaemia exist in inpatients with diabetes 'at risk' of hypoglycaemia (those on insulin and/or sulphonylureas), and if so whether patterns differ between hospitals and between these treatments.

Setting: Retrospective multicentre audit of inpatients with diabetes involving 11 acute UK NHS Trusts.

Participants: Capillary blood glucose readings of 3.9mmol/l or less (hypoglycaemia) for all inpatients with diabetes 'at risk' of hypoglycaemia were extracted from Abbott Precision Web Point-of-Care Data Management System™ over a four-week period. Overall 2,521 readings of 3.9mmol/l or less (hypoglycaemia) occurring in 866 subjects between 01/06/2013 and 29/06/2013 were analysed.

Interventions: Not applicable

Primary and secondary outcome measures: Not applicable

Results: The majority (65%) occurred between 21:00-08:59 hours, a pattern common to all Trusts. This was more frequent in sulphonylurea than insulin treated subjects (75.3% vs 59.3%, p=0.0001). Furthermore, hypoglycaemic readings were more frequent between 05:00-07:59 hours in sulphonylurea than insulin treated subjects (46.7% vs 22.7% of readings for respective treatments, p=0.0001). Sulphonylureas accounted for 31.8% of all hypoglycaemic readings. As a group, sulphonylurea treated subjects were older (median age 78 vs 73 years, p=0.0001) and had lower HbA1c [median 56mmol/mol (7.3%) vs 69mmol/mol (8.5%), p=0.0001]. Hypoglycaemic readings per subject were as frequent for sulphonylurea as for insulin treated subjects (median=2 for both) as were the proportion in each group with ≥5 readings (17.3% vs 17.7%).

Conclusions: In all Trusts hypoglycaemic readings were more frequent between 21:00-08:59 hours in 'at risk' inpatients with diabetes, with a greater frequency in the early morning period (05:00-07:59 hours) in sulphonylurea treated inpatients. This may have implications for the continuing use of sulphonylureas in the inpatient setting.

Trial registration: Not applicable.

Article summary:

Strengths and limitations of this study:

1. This study reports the burden of sulphonylurea related inpatient hypoglycaemia in NHS Trusts which has not been previously documented.
2. This study reports that the risk of hypoglycaemia appears to be greater in sulphonylurea treated inpatients than insulin treated inpatients in early morning hours.
3. This study confirms a previous single centre report that hypoglycaemia occurs more commonly at night-time/early morning in NHS Trusts participating in this study.
4. One of the limitations of this study was the inability to obtain the total number of inpatients with diabetes, type of diabetes and proportion of inpatients treated with insulin and sulphonylureas who did not experience hypoglycaemia.
5. Another limitation was that the detection of hypoglycaemic readings was strongly influenced by glucose monitoring frequency which was pre-determined.

Introduction:

Until recently tight glycaemic control in inpatients has been considered to be important in reducing morbidity and mortality as previous studies have shown that inpatient hyperglycaemia is associated with poorer outcomes (1, 2). However its advantages are offset by the risk of hypoglycaemia. Although the available data does not conclusively suggest that inpatient hypoglycaemia is an independent risk factor for mortality per se, there is increasing evidence that it is associated with increased mortality, morbidity and length of stay (3-5). In the NICE-SUGAR multinational randomised control trial severe hypoglycaemia was thirteen times more frequent in the intensively treated group (6.8% vs 0.5%, $p<0.001$) in which there was found to be a significantly higher ninety-day mortality compared to the conventional group (6). Subsequently, a meta-analysis that included the NICE-SUGAR data concluded that tight glycaemic control (with insulin therapy) increased the risk of hypoglycaemia with no overall mortality benefit (7). Indeed, some have suggested that hypoglycaemia should now be considered a new factor for cardiovascular risk (8).

The burden of inpatient hypoglycaemia in NHS hospitals has been well highlighted by the annual National Diabetes Inpatient Audit (NaDIA), the largest one week snapshot audit covering >95% of all acute NHS Trusts in England and Wales. In 2012, NaDIA reported that in England alone, 22.4% of inpatients experienced at least one hypoglycaemic episode [capillary blood glucose (CBG) ≤3.9mmol/l] and 2.2% had at least one hypoglycaemic episode that required rescue injectable therapy (9). Hypoglycaemia was significantly higher in those on insulin therapy; 45.3% of patients with type 1 diabetes and 31.8% of patients with type 2 diabetes treated with insulin had at least one episode of hypoglycaemia (9).

The American Diabetes Association (ADA) recommendation that insulin therapy in the form of a basal bolus regimen should be used as the preferred method of achieving and maintaining glycaemic control for all inpatients with diabetes has been widely adopted in the US (10). In the UK, there is no national consensus on the type of therapy that should be used for managing inpatients with diabetes who had not previously been on insulin i.e. whether oral agents be continued or there be a temporary switch to insulin therapy. Reluctance to adopt the ADA recommendation is supported by the frequency of drug errors and hypoglycaemia associated with insulin use from NaDIA data (9). However, to date, the extent of inpatient hypoglycaemia in the UK from the use of oral agents that can precipitate hypoglycaemia, namely sulphonylurea therapy is unknown.

In a recent study of inpatient hypoglycaemia in one NHS hospital, we found that more than two-thirds of all hypoglycaemic readings occurred between 21:00-08:59 hours (11). The current study was designed to determine whether similar or other temporal patterns of hypoglycaemia exist in other NHS hospitals and if so, to consider the possible reasons for any observed differences and potential preventative strategies. Additionally, in the previous study there appeared to be more hypoglycaemic readings in those on sulphonylurea therapy than anticipated, but that study was not specifically designed to examine this (11). As a result of this anecdotal observation and in view of the ADA's abandonment of sulphonylurea therapy in the inpatient setting, the current study was also designed to compare hypoglycaemic rates and patterns in sulphonylurea and insulin treated inpatients.

Methods:

The Joint British Diabetes Society (JBDS) recommends all adults with blood glucose ≤3.9mmol/l in hospitals be treated whether or not they are symptomatic (12). We therefore defined hypoglycaemia in our inpatient cohort as CBG ≤3.9mmol/l irrespective of the presence or absence of symptoms. Severe hypoglycaemia is usually defined as an episode of hypoglycaemia requiring third party assistance. This definition is not applicable to inpatients as most patients will not have direct access to carbohydrates and therefore require third party assistance from a health care professional even if the event was mild. We therefore used NaDIA 2012's biochemical classification of hypoglycaemia in which mild hypoglycaemia is defined as a CBG 3-3.9mmol/l and severe hypoglycaemia as a CBG ≤2.9mmol/l, irrespective of symptoms and necessity for third party assistance (9). Although not strictly correct, for the purpose of this study, we defined night-time hypoglycaemia as that between 21:00-08:59 hours and daytime hypoglycaemia as that between 09:00-20:59 hours.

The study was a four week retrospective multi-centre audit, undertaken between 01/06/13 and 29/06/13 in 11 NHS Trusts. Institutional approval was obtained from the audit department of each individual NHS Trust. All Trusts used Precision Xceed Pro™ as the only CBG monitoring system across the entire hospital. All CBG readings were relayed remotely to Precision Web Point-of-Care Data Management System™ (Abbott Diabetes Care Inc., Alameda, CA 94502, USA). From this database, all CBG readings of ≤3.9mmol/l were extracted at each NHS site including patients' unique identifiers, ward location, date and time of measurement. Each CBG reading of ≤3.9mmol/l was considered as an episode but

recurrent readings of ≤3.9mmol/l within 2 hours of a previously documented hypoglycaemic episode were automatically excluded as they could reflect re-testing for the same event.

We included adult (≥18 years) inpatients with diabetes 'at risk' of hypoglycaemia i.e. those treated with insulin and/or sulphonylureas. Data from Accident and Emergency departments, paediatric and day case areas were excluded. Age, length of stay until 15/07/13, type of therapy and HbA1c (within the preceding 3 months) data were collected from retrospective review of case records. Hospital bed numbers (excluding maternity and the previously mentioned areas) and factors that could influence institutional hypoglycaemia rates such as average weekly hours spent by diabetes specialist staff on inpatient diabetes care, meal timings, bedtime snack availability and frequency of CBG monitoring were obtained.

Statistics:

After completion of data collection, unique patient identifiers were removed and results were analysed using Microsoft Excel 2007, GraphPad and IBM SPSS Statistics v20. Descriptive statistics were used to evaluate characteristics of study subjects. Unpaired t test was used to compare means in parametric continuous data and Wilcoxon-Mann-Whitney test to compare non-parametric continuous data. Fisher's exact test was used to compare categorical data. Pearson correlation was used to evaluate linear correlation. All p values are two tailed and <0.05 was considered statistically significant.

Results:

Overall, 2,521 hypoglycaemic readings in 866 subjects from 11 NHS Trusts were analysed (Tables 1 and 2). Hypoglycaemia was exclusively attributable to sulphonylureas in 32.7% of all subjects who had recorded hypoglycaemia and accounted for 31.8% of all hypoglycaemic readings. In subjects exclusively treated with sulphonylurea therapy, 22.5% of readings were severe as opposed to 35.9% in insulin treated subjects. There was no difference in the percentage of subjects experiencing ≥5 hypoglycaemic readings between those treated with sulphonylureas and those on insulin therapy (17.3% vs 17.7%, p=0.923). Additionally, the number of hypoglycaemic readings per subject was the same for sulphonylurea and insulin treated subjects (median= 2 for both, p=0.888). Length of stay was similar between the two groups (median 11 vs 10 days, p=0.098). Subjects on sulphonylureas were significantly older (median age 78 vs 73 years, p=0.0001) and had lower HbA1c [median 56mmol/mol (7.3%) vs 69mmol/mol (8.5%), p=0.0001]. Length of stay correlated significantly with the number

of hypoglycaemic readings per subject for both insulin (r=0.286, p=0.0001) and sulphonylurea (r=0.167, p=0.005) treated subjects but did not correlate with age and HbA1c.

Temporal pattern analysis showed that hypoglycaemic readings were most frequent between 05:00-07:59 hours. Not surprisingly, the other frequent times coincided with glucose monitoring times i.e. before lunch, evening meal and bedtime. Interestingly, a significant number of hypoglycaemic readings occurred between 02:00-02:59 hours in all Trusts (even though routine 3am glucose monitoring was performed only by Trust 2). The observed patterns were similar in all Trusts (Figure 1). The relative frequency of hypoglycaemic readings between 05:00-07:59 hours in sulphonylurea treated subjects was twice that of the insulin treated subjects (46.7% vs 22.7%, p=0.0001), despite similar glucose monitoring frequency for both therapies (Figure 2). Overall, 65% of all hypoglycaemic readings occurred at night-time, ranging from 54.1% to 72.2% across the 11 Trusts. This was significantly greater in sulphonylurea compared to insulin treated subjects (75.3% vs 59.3%, p=0.0001). There was a positive correlation between proportion of night-time to daytime hypoglycaemic readings and proportion of hypoglycaemic readings attributable to sulphonylureas for each Trust (r=0.787, p=0.004). There was no significant difference in the number of hypoglycaemic readings per day between weekdays and weekends [mean (SD) 88.15±16.95 vs 84.22±12.16, p=0.538]. There was no relationship between the time reported to be spent by diabetes specialist nurses on inpatient care and hypoglycaemic readings per 100 bed ratio (r=-0.342, p=0.303).

Discussion:

Having expected to find variations in temporal patterns of hypoglycaemic readings related to differing clinical practices we found that all Trusts demonstrated the same pattern of hypoglycaemia as seen in the index hospital (11). We had previously postulated that prolonged fasting (14 hours) between evening meal and breakfast as well as the lack of bedtime carbohydrate snacks in the index hospital as important contributory factors. It is therefore of interest that all Trusts in this study reported similar prolonged fasting (13.5-15.5 hours) after the evening meal and that none guaranteed the provision of bedtime carbohydrate snacks. This feeding practice appears to be common in UK hospitals as reported in our previous online survey of NHS Trusts (11). We believe that addressing these meal timings and provision of bedtime carbohydrate snacks could reduce the frequency of hypoglycaemia in UK hospitals.

The second important finding was the extent of inpatient hypoglycaemia related to the use of sulphonylurea therapy. Whilst the burden of sulphonylurea related hypoglycaemia needing emergency medical assistance is increasingly recognised in the community setting (13-15), its contribution to inpatient hypoglycaemia appears not to have been fully appreciated. In this study we found that one third of hypoglycaemic readings were related to sulphonylurea therapy and indeed the frequency of inpatients experiencing markedly recurrent hypoglycaemia (≥5 hypoglycaemic readings) was the same as those receiving insulin. In a recent single centre report from one of the few US hospitals where oral agents continue to be used in the management of inpatient diabetes, one in five patients treated with sulphonylureas experienced at least one hypoglycaemic episode during their inpatient stay (16). In our study it was not possible to determine this as the initial source data was hypoglycaemic readings recorded in the Precision Web Point-of-Care Data Management System™ and therefore the total number of inpatients with diabetes was not known. In addition, for the same reason, it was not possible determine whether those with low eGFR had more hypoglycaemia, nor whether different insulin regimes were associated with greater risk.

There are a number of factors that may contribute to frequent hypoglycaemia in inpatients on sulphonylurea therapy. Health care professionals have greater concern for insulin treated inpatients than those on tablets who are often considered to have less severe diabetes and therefore perceived less likely to suffer hypoglycaemia. Physicians, nurses and even the small subgroup of patients who self-manage their diabetes in hospital are less inclined to adjust doses of oral hypoglycaemic agents than insulin even during periods of varying meal intake. This is reflected in the TOPDOC study of UK trainee-doctors, who when given an example of a patient with poor control, were less likely to alter the dose of oral agents compared to insulin (65% vs 79%) (17). Finally, the pharmacokinetic profile of sulphonylureas are less predictable compared to insulin especially in the complex inpatient setting with changing nutritional status, renal function etc.

In the US, insulin therapy is the preferred treatment for all inpatients with diabetes (10). The basal-bolus system, utilising well tested insulin regimens such as the RABBIT medical and surgical protocols are extensively used and have been shown to be associated with low frequencies of inpatient hypoglycaemia (18, 19). It is unlikely that such regimens will be adopted in the UK in the near future as this would require transferring up to one in six

inpatients with diabetes to basal-bolus insulin therapy, when at present the expertise for initiating and monitoring inpatients on insulin therapy is very limited. Thus, NaDIA 2012 found that 32.2% of NHS England Trusts did not have a dedicated diabetes inpatient specialist nurse (9). Secondly, very serious concerns have been raised on the safe use of insulin in inpatients in UK (20-22). The National Patient Safety Agency identified 16,600 reported incidents involving insulin between November 2003 and November 2009, the majority occurring in inpatients; 24% caused harm to the patient and there were 18 individual incidences associated with fatal or severe outcomes (22). Importantly these figures represent the tip of the iceberg as it is recognised that such errors are grossly under-reported in the UK. Thus, in contrast, NaDIA 2012 found that in England 21.8% of inpatients with diabetes treated with insulin therapy in the week of the audit had one or more insulin errors, summating to one hundred and fifty thousand errors each year (9). Furthermore, in a recent retrospective survey of diabetes inpatient teams at least twelve episodes of serious harm related to inpatient hypoglycaemia (including death, cardiac arrest and irreversible brain injury) were reported to have occurred in the 41 UK Trusts who participated in the survey covering a twelve month period. Insulin therapy was implicated in at least ten of these events (23). It is hoped that in the future electronic prescribing and clinical decision support systems will help to minimise these errors while recognising that such systems are not infallible and will not prevent errors in insulin administration nor in management decisions (24, 25).

Finally, one of the aims of this multi-site study was to identify and learn from differences between Trusts. Trust 2 had the lowest frequency of both mild and severe hypoglycaemia per 100 beds and the lowest number of recurrent hypoglycaemic readings. It may be relevant that this Trust introduced a number of changes in practice to reduce their institutional hypoglycaemia rates following a fatal adverse event related to inpatient hypoglycaemia. These included intentionally relaxing inpatient glycaemic targets to 7-11mmol/l in comparison with the currently recommended acceptable range of 4-12mmol/l (26), introducing an aggressive capillary glucose monitoring regimen including 3am glucose testing (the only trust to do so) and implementing intensive education programs for nursing and medical staff achieved by increasing the number of inpatient diabetes specialist nurses and their time devoted to inpatient care (Table 1). Whether replicating these practices in other Trusts would lead to reductions in their institutional hypoglycaemia rates can only be speculated.

We recognise several limitations to our study. The source data was the Precision Web Point-of-Care Data Management System™; as a result we were unable to obtain the total number of inpatients with diabetes, a breakdown by type of diabetes, and the proportions treated with insulin and sulphonylureas who did not experience hypoglycaemia. Therefore, we were unable to calculate the exact risk with each therapy per se. The detection of hypoglycaemic readings was strongly influenced by glucose monitoring frequency which was pre-determined and similar in all hospitals; occurring at meal times and bedtime. Continuous glucose monitoring would almost certainly reveal an even greater frequency of hypoglycaemic readings, especially at night-time when patients are not routinely monitored. As previously mentioned while hospital meal times may be a major contributory factor for the frequency of night-time and early morning hypoglycaemia, we acknowledge that we did not consider other important factors for hypoglycaemia in hospitalised patients such as sepsis, renal and liver disease, overall nutritional status and changing drug therapies such as tapering of steroid therapy. Despite these limitations we believe that this study provides important information on institutional patterns of inpatient hypoglycaemia in the 'at risk' inpatients and the impact of sulphonylurea therapies.

In summary in UK hospitals, hypoglycaemia is detected more frequently during the period between 21:00-08:59 hours (night-time), and sulphonylurea therapy appears to present a greater risk than insulin particularly between 05:00-07:59 hours (early morning). Institutional feeding patterns appear to be contributory but further work is required to determine whether a change in meal times would reduce institutional hypoglycaemia rates. Importantly, our findings may have implications for the continued use of sulphonylureas in the UK in the inpatient setting.

What is already known on this topic?

A single NHS Trust previously reported that hypoglycaemia was more frequent at night-time in hospitalised patients.

It was not known whether this pattern was common in other NHS Trusts.

The burden of inpatient hypoglycaemia due to sulphonylurea therapy was not previously known in NHS Trusts.

What this study adds:

Hypoglycaemia is detected more commonly at night-time/early morning in all participating NHS Trusts.

Similar problems with institutional feeding patterns exist in all participating NHS Trusts.

There is a substantial burden of sulphonylurea related inpatient hypoglycaemia and it appears to present a greater risk than insulin therapy in early morning hours.

These observations should lead to a review of feeding times and the use of sulphonylureas in hospitalised patients.

Figure legends:

Figure 1: Temporal patterns of hypoglycaemic readings over the 24 hour period in the individual 11 NHS Trusts. The x axis represent the time period, for e.g. 0 represents the time period between 00:00 and 00:59 hours, 1 represents the time period between 01:00 and 01:59 hours etc. The y axis represents the number of hypoglycaemic readings occurring in that time period. The figure demonstrates very similar temporal patterns for all Trusts.

Figure 2: Temporal patterns of hypoglycaemic readings over the 24 hour period in all subjects on insulin, sulphonylureas and both. The x axis represent the time period, for e.g. 0 represents the time period between 00:00 and 00:59 hours, 1 represents the time period between 01:00 and 01:59 hours etc. The y axis represents the number of hypoglycaemic readings occurring in that time period. The figure demonstrates that the highest frequency occurs between 05:00 to 07:59 hours for both insulin and sulphonylurea therapies. .

Table 1: Table represents individual data from the 11 NHS Trusts.

Table 2: Table shows combined data from all Trusts for subjects on insulin, sulphonylureas or both forms of therapy.

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Declaration of competing interests:

All three authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: the MaGIC study group meetings were sponsored by Abbott, UK who also assisted in extraction of data from Precision Web Point-of-Care Data Management System™ but was not involved in the design or origin of the study, nor in funding or influencing the analysis, nor in interpretation or reporting of the data nor in the preparation of this manuscript; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Transparency declaration statement:

The lead author RR (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data sharing statement:

No additional data is available.

Contributorship

RR designed data collection tools, monitored data collection, cleaned and analysed the data, drafted and revised the paper. He is the guarantor. CK assisted in data collection and revised the draft paper. GR initiated the audit, monitored data collection, drafted and revised the paper and was the lead for the audit.

Collaborators

All other members of MaGIC study group designed the audit, assisted in data collection and revised the draft paper. The following are members of the MaGIC (Managing Glycaemia using Innovations in Care) study group (UK): Gerry Rayman (Group lead, The Ipswich

Hospital NHS Trust), Rajesh Rajendran (The Ipswich Hospital NHS Trust), Chris Kerry (The Ipswich Hospital NHS Trust), Ainslie Lang (Royal United Hospital Bath NHS Trust), James Young (Worcestershire Acute Hospitals NHS Trust), Lisa Smith (Worcestershire Acute Hospitals NHS Trust), Jane Wilson (Worcestershire Acute Hospitals NHS Trust), Erwin Castro (East Essex Healthcare NHS Trust), Valerie Edwards (East Essex Healthcare NHS Trust), Fathi Abourawi (Northern Lincolnshire and Goole Hospitals NHS Foundation Trust), Caroline Andrews (Northern Lincolnshire and Goole Hospitals NHS Foundation Trust), Francesca Swords (Norfolk and Norwich University Hospitals NHS Foundation Trust), Michelle Nation (The Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust), Beverley Eaglesfield (Derby Hospitals NHS Foundation Trust), Anne Lee (Derby Hospitals NHS Foundation Trust), Kim Heathcote (NHS Dumfries and Galloway), Fiona Green (NHS Dumfries and Galloway), Louise Clark (NHS Dumfries and Galloway), Jenny Tringham (Frimley Park Hospital NHS Foundation Trust), Laura Dinning (Harrogate and District NHS Foundation Trust) and Peter Hammond (Harrogate and District NHS Foundation Trust).

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Variable	Each individual Trust data	Combined

		1	2	3	4	5	6	7	8	9	10	11	
Number of beds*		537	690	344	264	449	939	680	997	274	690	293	6157
Diabetes Inpatient Specialist Nurse time devoted to inpatient diabetes care†		75.5	97	30	20	20	78	75	52	10	32	48.5	538
Number of 'at risk' subjects	All	85	82	40	43	67	156	73	155	50	74	41	866
	Insulin	50	56	26	18	39	103	44	96	29	52	28	541
	Sulphonylurea	32	25	12	22	24	44	22	52	18	20	12	283
	Both‡	3	1	2	3	4	9	7	7	3	2	1	42
Number of hypoglycaemic readings	All	334	163	136	115	264	432	234	316	159	198	170	2521
	Insulin	219	107	90	61	161	257	161	199	96	118	125	1594
	Sulphonylurea	105	55	34	51	89	154	61	104	46	68	34	801
	Both‡	10	1	12	3	14	21	12	13	17	12	11	126
	Mild hypoglycaemia	239	124	86	81	177	309	165	203	103	134	108	1729
	Severe hypoglycaemia	95	39	50	34	87	123	69	113	56	64	62	792
Hypoglycaemia per 100 bed ratio§	All	62.2	23.6	39.5	43.6	58.8	46	34.4	31.7	58	28.7	58	41
	Mild hypoglycaemia	44.5	18	25	30.7	39.4	32.9	24.3	20.4	37.6	19.4	36.9	28.1
	Severe hypoglycaemia	17.7	5.6	14.5	12.9	19.4	13.1	10.1	11.3	20.4	9.3	21.1	12.9
Hypoglycaemic readings per subject	Median	2	1	2	2	3	2	2	2	2	1	2	2
	Mean	3.93	1.99	3.4	2.7	3.94	2.77	3.21	2.04	3.18	2.68	4.15	2.91
	Range	1-29	1-9	1-11	1-23	1-18	1-16	1-13	1-11	1-12	1-14	1-30	1-30
Subjects with ≥5 readings of hypoglycaemia during the study period		20	7	10	5	18	27	15	15	11	15	11	154
Frequency of glucose monitoring	Insulin	BD-QDS	QDS and 3am	QDS	QDS	BD-QDS	QDS	QDS	QDS	QDS	QDS	QDS	-
	Sulphonylurea	BD-QDS	QDS and 3am	BD-QDS	BD	BD-QDS	BD-QDS	QDS	BD-QDS	QDS	OD-QDS	QDS	-
Hospital meal timings	Breakfast	7:30	7:00	7:00 - 8:00	8:30	7:30 - 8:30	7:00 - 9:00	7:30 - 8:30	7:45 - 8:30	7:45 - 8:30	7:00 - 8:00	8:00	-
	Afternoon meal	12:00	12:00	12:00-13:00	12:15	12:00-13:00	12:00-14:00	11:30-12:45	12:00-13:00	12:00-13:00	12:00-13:00	12:00	-
	Evening meal	17:00	17:00	18:00-19:00	17:00	17:00-18:00	17:00-19:00	16:30-17:45	17:00-18:00	17:00-18:00	17:00-18:00	17:00	-
Time period of hypoglycaemic readings													
Daytime	09:00-14:59	75	30	25	8	33	61	45	46	25	14	31	393
	15:00-20:59	50	33	29	25	51	78	46	65	24	41	47	489
	09:00-20:59	125	63	54	33	84	139	91	111	49	55	78	882
Night-time	21:00-02:59	93	36	36	34	69	133	68	76	45	51	45	686
	03:00-08:59	116	64	46	48	111	160	75	129	65	92	47	953
	21:00-08:59	209	100	82	82	180	293	143	205	110	143	92	1639
Percentage of night-time hypoglycaemia		62.6	61.3	60.3	71.3	68.2	67.8	61.1	64.9	69.2	72.2	54.1	65

*Bed numbers exclude paediatric, maternity and day case units

†Average Diabetes Inpatient Specialist Nurse time (hours per week) devoted to inpatient diabetes care

‡Subjects on both insulin and sulphonylurea therapy

§Calculated as 100 * number of hypoglycaemic readings ÷ number of beds

No Trust guaranteed the provision of a bedtime snack for inpatients with diabetes

Table 1:

Table 2:

Variable		All	Insulin	Sulphonylurea	Both Insulin and Sulphonylureas
Number of subjects		866	541	283	42
Number of hypoglycaemic readings (%)	All	2521	1594	801	126
	Severe hypoglycaemia	792 (31.4)	572 (35.9)	180 (22.5)	40 (31.7)
	Mild hypoglycaemia	1729 (68.6)	1022 (64.1)	621 (77.5)	86 (68.3)
Subjects with ≥5 readings of hypoglycaemia per subject during the study period (%)		154 (17.8)	96 (17.7)	49 (17.3)	9 (21.4)
			p=0.923		
Number of hypoglycaemic readings per subject	Mean±SD (Range)	2.91±3.16 (1-30)	2.95±3.29 (1-30)	2.83±2.89 (1-29)	3±3.21 (1-12)
	Median (Interquartile range)	2 (1-3)	2 (1-3)	2 (1-4)	1 (1-3.25)
			p=0.888		
Age (years)	Mean±SD (Range)	71±16 (18-98)	67±18 (18-97)	76±10 (42-98)	75±9 (46-91)
	Median (Interquartile range)	75 (64-82)	73 (56-81)	78 (70-83)	77 (69-81)
			p=0.0001		
HbA1c in mmol/mol (%)	Mean [Range]	n=575*	n=364*	n=181*	n=30*
		69(8.5) [28(4.7)-177(18.3)]	73(8.8) [28(4.7)-177(18.3)]	60(7.6) [33(5.2)-161(16.9)]	73(8.8) [46(6.4)-115(12.7)]
	Median [Interquartile range]	64(8) [53(7)-80(9.5)]	69(8.5) [56(7.3)-83(9.7)]	56(7.3) (47(6.5)-66(8.2)]	73(8.8) [55(7.2)-86(10)]
			p=0.0001		
Length of stay (days)	Mean±SD (Range)	n=862*	n=540*	n=282*	n=40*
		17±17.1 (1-101)	16.1±17 (1-101)	17±16.2 (1-100)	25±21.9 (1-82)
	Median (Interquartile range)	11 (5-22)	10 (4-21)	11 (6-23)	20 (7-45)
			p=0.098		
Temporal pattern of hypoglycaemic readings					
Daytime hypoglycaemia	09:00-14:59	393	296	84	13
	15:00-20:59	489	352	114	23
	Total 09:00-20:59	882	648	198	36
Night-time hypoglycaemia (%)	21:00-02:59	686	478	179	29
	03:00-08:59	953	468	424	61
	Total 21:00-08:59	1639 (65)	946 (59.3)	603 (75.3)	90 (71.4)
			p=0.0001		

*Subjects in whom data available

Original article:

Title:

Temporal patterns of hypoglycaemia and burden of sulphonylurea related hypoglycaemia in UK hospitals: a retrospective multi-centre audit of hospitalised patients with diabetes

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Abstract:

Objectives: To determine whether temporal patterns of hypoglycaemia exist in inpatients with diabetes 'at risk' of hypoglycaemia (those on insulin and/or sulphonylureas), and if so whether patterns differ between hospitals and between these treatments.

Setting: Retrospective multicentre audit of inpatients with diabetes involving 11 acute UK NHS Trusts.

Participants: Capillary blood glucose readings of 3.9mmol/l or less (hypoglycaemia) for all inpatients with diabetes 'at risk' of hypoglycaemia were extracted from Abbott Precision Web Point-of-Care Data Management System™ over a four-week period. Overall 2,521 readings of 3.9mmol/l or less (hypoglycaemia) occurring in 866 subjects between 01/06/2013 and 29/06/2013 were analysed.

Interventions: Not applicable

Primary and secondary outcome measures: Not applicable

Results: The majority (65%) occurred between 21:00-08:59 hours, a pattern common to all Trusts. This was more frequent in sulphonylurea than insulin treated subjects (75.3% vs 59.3%, p=0.0001). Furthermore, hypoglycaemic readings were more frequent between 05:00-07:59 hours in sulphonylurea than insulin treated subjects (46.7% vs 22.7% of readings for respective treatments, p=0.0001). Sulphonylureas accounted for 31.8% of all hypoglycaemic readings. As a group, sulphonylurea treated subjects were older (median age 78 vs 73 years, p=0.0001) and had lower HbA1c [median 56mmol/mol (7.3%) vs 69mmol/mol (8.5%), p=0.0001]. Hypoglycaemic readings per subject were as frequent for sulphonylurea as for insulin treated subjects (median=2 for both) as were the proportion in each group with ≥5 readings (17.3% vs 17.7%).

Conclusions: In all Trusts hypoglycaemic readings were more frequent between 21:00-08:59 hours in 'at risk' inpatients with diabetes, with a greater frequency in the early morning period (05:00-07:59 hours) in sulphonylurea treated inpatients. This may have implications for the continuing use of sulphonylureas in the inpatient setting.

Trial registration: Not applicable.

Article summary:

Strengths and limitations of this study:

1. This study reports the burden of sulphonylurea related inpatient hypoglycaemia in NHS Trusts which has not been previously documented.
2. This study reports that the risk of hypoglycaemia appears to be greater in sulphonylurea treated inpatients than insulin treated inpatients in early morning hours.
3. This study confirms a previous single centre report that hypoglycaemia occurs more commonly at night-time/early morning in NHS Trusts participating in this study.
4. One of the limitations of this study was the inability to obtain the total number of inpatients with diabetes, type of diabetes and proportion of inpatients treated with insulin and sulphonylureas who did not experience hypoglycaemia.
5. Another limitation was that the detection of hypoglycaemic readings was strongly influenced by glucose monitoring frequency which was pre-determined.

Introduction:

Until recently tight glycaemic control in inpatients has been considered to be important in reducing morbidity and mortality as previous studies have shown that inpatient hyperglycaemia is associated with poorer outcomes (1, 2). However its advantages are offset by the risk of hypoglycaemia. Although the available data does not conclusively suggest that inpatient hypoglycaemia is an independent risk factor for mortality per se, there is increasing evidence that it is associated with increased mortality, morbidity and length of stay (3-5). In the NICE-SUGAR multinational randomised control trial severe hypoglycaemia was thirteen times more frequent in the intensively treated group (6.8% vs 0.5%, $p<0.001$) in which there was found to be a significantly higher ninety-day mortality compared to the conventional group (6). Subsequently, a meta-analysis that included the NICE-SUGAR data concluded that tight glycaemic control (with insulin therapy) increased the risk of hypoglycaemia with no overall mortality benefit (7). Indeed, some have suggested that hypoglycaemia should now be considered a new factor for cardiovascular risk (8).

The burden of inpatient hypoglycaemia in NHS hospitals has been well highlighted by the annual National Diabetes Inpatient Audit (NaDIA), the largest one week snapshot audit covering >95% of all acute NHS Trusts in England and Wales. In 2012, NaDIA reported that in England alone, 22.4% of inpatients experienced at least one hypoglycaemic episode [capillary blood glucose (CBG) ≤3.9mmol/l] and 2.2% had at least one hypoglycaemic episode that required rescue injectable therapy (9). Hypoglycaemia was significantly higher in those on insulin therapy; 45.3% of patients with type 1 diabetes and 31.8% of patients with type 2 diabetes treated with insulin had at least one episode of hypoglycaemia (9).

The American Diabetes Association (ADA) recommendation that insulin therapy in the form of a basal bolus regimen should be used as the preferred method of achieving and maintaining glycaemic control for all inpatients with diabetes has been widely adopted in the US (10). In the UK, there is no national consensus on the type of therapy that should be used for managing inpatients with diabetes who had not previously been on insulin i.e. whether oral agents be continued or there be a temporary switch to insulin therapy. Reluctance to adopt the ADA recommendation is supported by the frequency of drug errors and hypoglycaemia associated with insulin use from NaDIA data (9). However, to date, the extent of inpatient hypoglycaemia in the UK from the use of oral agents that can precipitate hypoglycaemia, namely sulphonylurea therapy is unknown.

In a recent study of inpatient hypoglycaemia in one NHS hospital, we found that more than two-thirds of all hypoglycaemic readings occurred between 21:00-08:59 hours (11). The current study was designed to determine whether similar or other temporal patterns of hypoglycaemia exist in other NHS hospitals and if so, to consider the possible reasons for any observed differences and potential preventative strategies. Additionally, in the previous study there appeared to be more hypoglycaemic readings in those on sulphonylurea therapy than anticipated, but that study was not specifically designed to examine this (11). As a result of this anecdotal observation and in view of the ADA's abandonment of sulphonylurea therapy in the inpatient setting, the current study was also designed to compare hypoglycaemic rates and patterns in sulphonylurea and insulin treated inpatients.

Methods:

The Joint British Diabetes Society (JBDS) recommends all adults with blood glucose ≤3.9mmol/l in hospitals be treated whether or not they are symptomatic (12). We therefore defined hypoglycaemia in our inpatient cohort as CBG ≤3.9mmol/l irrespective of the presence or absence of symptoms. Severe hypoglycaemia is usually defined as an episode of hypoglycaemia requiring third party assistance. This definition is not applicable to inpatients as most patients will not have direct access to carbohydrates and therefore require third party assistance from a health care professional even if the event was mild. We therefore used NaDIA 2012's biochemical classification of hypoglycaemia in which mild hypoglycaemia is defined as a CBG 3-3.9mmol/l and severe hypoglycaemia as a CBG ≤2.9mmol/l, irrespective of symptoms and necessity for third party assistance (9). Although not strictly correct, for the purpose of this study, we defined night-time hypoglycaemia as that between 21:00-08:59 hours and daytime hypoglycaemia as that between 09:00-20:59 hours.

The study was a four week retrospective multi-centre audit, undertaken between 01/06/13 and 29/06/13 in 11 NHS Trusts. Institutional approval was obtained from the audit department of each individual NHS Trust. All Trusts used Precision Xceed Pro™ as the only CBG monitoring system across the entire hospital. All CBG readings were relayed remotely to Precision Web Point-of-Care Data Management System™ (Abbott Diabetes Care Inc., Alameda, CA 94502, USA). From this database, all CBG readings of ≤3.9mmol/l were extracted at each NHS site including patients' unique identifiers, ward location, date and time of measurement. Each CBG reading of ≤3.9mmol/l was considered as an episode but

recurrent readings of ≤3.9mmol/l within 2 hours of a previously documented hypoglycaemic episode were automatically excluded as they could reflect re-testing for the same event.

We included adult (≥18 years) inpatients with diabetes 'at risk' of hypoglycaemia i.e. those treated with insulin and/or sulphonylureas. Data from Accident and Emergency departments, paediatric and day case areas were excluded. Age, length of stay until 15/07/13, type of therapy and HbA1c (within the preceding 3 months) data were collected from retrospective review of case records. Hospital bed numbers (excluding maternity and the previously mentioned areas) and factors that could influence institutional hypoglycaemia rates such as average weekly hours spent by diabetes specialist staff on inpatient diabetes care, meal timings, bedtime snack availability and frequency of CBG monitoring were obtained.

Statistics:

After completion of data collection, unique patient identifiers were removed and results were analysed using Microsoft Excel 2007, GraphPad and IBM SPSS Statistics v20. Descriptive statistics were used to evaluate characteristics of study subjects. Unpaired t test was used to compare means in parametric continuous data and Wilcoxon-Mann-Whitney test to compare non-parametric continuous data. Fisher's exact test was used to compare categorical data. Pearson correlation was used to evaluate linear correlation. All p values are two tailed and <0.05 was considered statistically significant.

Results:

Overall, 2,521 hypoglycaemic readings in 866 subjects from 11 NHS Trusts were analysed (Tables 1 and 2). Hypoglycaemia was exclusively attributable to sulphonylureas in 32.7% of all subjects who had recorded hypoglycaemia and accounted for 31.8% of all hypoglycaemic readings. In subjects exclusively treated with sulphonylurea therapy, 22.5% of readings were severe as opposed to 35.9% in insulin treated subjects. There was no difference in the percentage of subjects experiencing ≥5 hypoglycaemic readings between those treated with sulphonylureas and those on insulin therapy (17.3% vs 17.7%, p=0.923). Additionally, the number of hypoglycaemic readings per subject was the same for sulphonylurea and insulin treated subjects (median= 2 for both, p=0.888). Length of stay was similar between the two groups (median 11 vs 10 days, p=0.098). Subjects on sulphonylureas were significantly older (median age 78 vs 73 years, p=0.0001) and had lower HbA1c [median 56mmol/mol (7.3%) vs 69mmol/mol (8.5%), p=0.0001]. Length of stay correlated significantly with the number

of hypoglycaemic readings per subject for both insulin (r=0.286, p=0.0001) and sulphonylurea (r=0.167, p=0.005) treated subjects but did not correlate with age and HbA1c.

Temporal pattern analysis showed that hypoglycaemic readings were most frequent between 05:00-07:59 hours. Not surprisingly, the other frequent times coincided with glucose monitoring times i.e. before lunch, evening meal and bedtime. Interestingly, a significant number of hypoglycaemic readings occurred between 02:00-02:59 hours in all Trusts (even though routine 3am glucose monitoring was performed only by Trust 2). The observed patterns were similar in all Trusts (Figure 1). The relative frequency of hypoglycaemic readings between 05:00-07:59 hours in sulphonylurea treated subjects was twice that of the insulin treated subjects (46.7% vs 22.7%, p=0.0001), despite similar glucose monitoring frequency for both therapies (Figure 2). Overall, 65% of all hypoglycaemic readings occurred at night-time, ranging from 54.1% to 72.2% across the 11 Trusts. This was significantly greater in sulphonylurea compared to insulin treated subjects (75.3% vs 59.3%, p=0.0001). There was a positive correlation between proportion of night-time to daytime hypoglycaemic readings and proportion of hypoglycaemic readings attributable to sulphonylureas for each Trust (r=0.787, p=0.004). There was no significant difference in the number of hypoglycaemic readings per day between weekdays and weekends [mean (SD) 88.15±16.95 vs 84.22±12.16, p=0.538]. There was no relationship between the time reported to be spent by diabetes specialist nurses on inpatient care and hypoglycaemic readings per 100 bed ratio (r=-0.342, p=0.303).

Discussion:

Having expected to find variations in temporal patterns of hypoglycaemic readings related to differing clinical practices we found that all Trusts demonstrated the same pattern of hypoglycaemia as seen in the index hospital (11). We had previously postulated that prolonged fasting (14 hours) between evening meal and breakfast as well as the lack of bedtime carbohydrate snacks in the index hospital as important contributory factors. It is therefore of interest that all Trusts in this study reported similar prolonged fasting (13.5-15.5 hours) after the evening meal and that none guaranteed the provision of bedtime carbohydrate snacks. This feeding practice appears to be common in UK hospitals as reported in our previous online survey of NHS Trusts (11). We believe that addressing these meal timings and provision of bedtime carbohydrate snacks could reduce the frequency of hypoglycaemia in UK hospitals.

The second important finding was the extent of inpatient hypoglycaemia related to the use of sulphonylurea therapy. Whilst the burden of sulphonylurea related hypoglycaemia needing emergency medical assistance is increasingly recognised in the community setting (13-15), its contribution to inpatient hypoglycaemia appears not to have been fully appreciated. In this study we found that one third of hypoglycaemic readings were related to sulphonylurea therapy and indeed the frequency of inpatients experiencing markedly recurrent hypoglycaemia (≥5 hypoglycaemic readings) was the same as those receiving insulin. In a recent single centre report from one of the few US hospitals where oral agents continue to be used in the management of inpatient diabetes, one in five patients treated with sulphonylureas experienced at least one hypoglycaemic episode during their inpatient stay (16). In our study it was not possible to determine this as the initial source data was hypoglycaemic readings recorded in the Precision Web Point-of-Care Data Management System™ and therefore the total number of inpatients with diabetes was not known. In addition, for the same reason, it was not possible determine whether those with low eGFR had more hypoglycaemia, nor whether different insulin regimes were associated with greater risk.

There are a number of factors that may contribute to frequent hypoglycaemia in inpatients on sulphonylurea therapy. Health care professionals have greater concern for insulin treated inpatients than those on tablets who are often considered to have less severe diabetes and therefore perceived less likely to suffer hypoglycaemia. Physicians, nurses and even the small subgroup of patients who self-manage their diabetes in hospital are less inclined to adjust doses of oral hypoglycaemic agents than insulin even during periods of varying meal intake. This is reflected in the TOPDOC study of UK trainee-doctors, who when given an example of a patient with poor control, were less likely to alter the dose of oral agents compared to insulin (65% vs 79%) (17). Finally, the pharmacokinetic profile of sulphonylureas are less predictable compared to insulin especially in the complex inpatient setting with changing nutritional status, renal function etc.

In the US, insulin therapy is the preferred treatment for all inpatients with diabetes (10). The basal-bolus system, utilising well tested insulin regimens such as the RABBIT medical and surgical protocols are extensively used and have been shown to be associated with low frequencies of inpatient hypoglycaemia (18, 19). It is unlikely that such regimens will be adopted in the UK in the near future as this would require transferring up to one in six

inpatients with diabetes to basal-bolus insulin therapy, when at present the expertise for initiating and monitoring inpatients on insulin therapy is very limited. Thus, NaDIA 2012 found that 32.2% of NHS England Trusts did not have a dedicated diabetes inpatient specialist nurse (9). Secondly, very serious concerns have been raised on the safe use of insulin in inpatients in UK (20-22). The National Patient Safety Agency identified 16,600 reported incidents involving insulin between November 2003 and November 2009, the majority occurring in inpatients; 24% caused harm to the patient and there were 18 individual incidences associated with fatal or severe outcomes (22). Importantly these figures represent the tip of the iceberg as it is recognised that such errors are grossly under-reported in the UK. Thus, in contrast, NaDIA 2012 found that in England 21.8% of inpatients with diabetes treated with insulin therapy in the week of the audit had one or more insulin errors, summating to one hundred and fifty thousand errors each year (9). Furthermore, in a recent retrospective survey of diabetes inpatient teams at least twelve episodes of serious harm related to inpatient hypoglycaemia (including death, cardiac arrest and irreversible brain injury) were reported to have occurred in the 41 UK Trusts who participated in the survey covering a twelve month period. Insulin therapy was implicated in at least ten of these events (23). It is hoped that in the future electronic prescribing and clinical decision support systems will help to minimise these errors while recognising that such systems are not infallible and will not prevent errors in insulin administration nor in management decisions (24, 25).

Finally, one of the aims of this multi-site study was to identify and learn from differences between Trusts. Trust 2 had the lowest frequency of both mild and severe hypoglycaemia per 100 beds and the lowest number of recurrent hypoglycaemic readings. It may be relevant that this Trust introduced a number of changes in practice to reduce their institutional hypoglycaemia rates following a fatal adverse event related to inpatient hypoglycaemia. These included intentionally relaxing inpatient glycaemic targets to 7-11mmol/l in comparison with the currently recommended acceptable range of 4-12mmol/l (26), introducing an aggressive capillary glucose monitoring regimen including 3am glucose testing (the only trust to do so) and implementing intensive education programs for nursing and medical staff achieved by increasing the number of inpatient diabetes specialist nurses and their time devoted to inpatient care (Table 1). Whether replicating these practices in other Trusts would lead to reductions in their institutional hypoglycaemia rates can only be speculated.

We recognise several limitations to our study. The source data was the Precision Web Point-of-Care Data Management System™; as a result we were unable to obtain the total number of inpatients with diabetes, a breakdown by type of diabetes, and the proportions treated with insulin and sulphonylureas who did not experience hypoglycaemia. Therefore, we were unable to calculate the exact risk with each therapy per se. The detection of hypoglycaemic readings was strongly influenced by glucose monitoring frequency which was pre-determined and similar in all hospitals; occurring at meal times and bedtime. Continuous glucose monitoring would almost certainly reveal an even greater frequency of hypoglycaemic readings, especially at night-time when patients are not routinely monitored. As previously mentioned while hospital meal times may be a major contributory factor for the frequency of night-time and early morning hypoglycaemia, we acknowledge that we did not consider other important factors for hypoglycaemia in hospitalised patients such as sepsis, renal and liver disease, overall nutritional status and changing drug therapies such as tapering of steroid therapy. Despite these limitations we believe that this study provides important information on institutional patterns of inpatient hypoglycaemia in the 'at risk' inpatients and the impact of sulphonylurea therapies.

In summary in UK hospitals, hypoglycaemia is detected more frequently during the period between 21:00-08:59 hours (night-time), and sulphonylurea therapy appears to present a greater risk than insulin particularly between 05:00-07:59 hours (early morning). Institutional feeding patterns appear to be contributory but further work is required to determine whether a change in meal times would reduce institutional hypoglycaemia rates. Importantly, our findings may have implications for the continued use of sulphonylureas in the UK in the inpatient setting.

What is already known on this topic?

A single NHS Trust previously reported that hypoglycaemia was more frequent at night-time in hospitalised patients.

It was not known whether this pattern was common in other NHS Trusts.

The burden of inpatient hypoglycaemia due to sulphonylurea therapy was not previously known in NHS Trusts.

What this study adds:

Hypoglycaemia is detected more commonly at night-time/early morning in all participating NHS Trusts.

Similar problems with institutional feeding patterns exist in all participating NHS Trusts.

There is a substantial burden of sulphonylurea related inpatient hypoglycaemia and it appears to present a greater risk than insulin therapy in early morning hours.

These observations should lead to a review of feeding times and the use of sulphonylureas in hospitalised patients.

Figure legends:

Figure 1: Temporal patterns of hypoglycaemic readings over the 24 hour period in the individual 11 NHS Trusts. The x axis represent the time period, for e.g. 0 represents the time period between 00:00 and 00:59 hours, 1 represents the time period between 01:00 and 01:59 hours etc. The y axis represents the number of hypoglycaemic readings occurring in that time period. The figure demonstrates very similar temporal patterns for all Trusts.

Figure 2: Temporal patterns of hypoglycaemic readings over the 24 hour period in all subjects on insulin, sulphonylureas and both. The x axis represent the time period, for e.g. 0 represents the time period between 00:00 and 00:59 hours, 1 represents the time period between 01:00 and 01:59 hours etc. The y axis represents the number of hypoglycaemic readings occurring in that time period. The figure demonstrates that the highest frequency occurs between 05:00 to 07:59 hours for both insulin and sulphonylurea therapies. .

Table 1: Table represents individual data from the 11 NHS Trusts.

Table 2: Table shows combined data from all Trusts for subjects on insulin, sulphonylureas or both forms of therapy.

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Declaration of competing interests:

All three authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: the MaGIC study group meetings were sponsored by Abbott, UK who also assisted in extraction of data from Precision Web Point-of-Care Data Management System™ but was not involved in the design or origin of the study, nor in funding or influencing the analysis, nor in interpretation or reporting of the data nor in the preparation of this manuscript; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Transparency declaration statement:

The lead author RR (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data sharing statement:

No additional data is available.

Contributorship and authorship statement:

RR designed data collection tools, monitored data collection, cleaned and analysed the data, drafted and revised the paper. He is the guarantor. CK assisted in data collection and revised the draft paper. GR initiated the audit, monitored data collection, drafted and revised the paper and was the lead for the audit. All other members of MaGIC study group designed the audit, assisted in data collection and revised the draft paper. The following are members of the MaGIC (Managing Glycaemia using Innovations in Care) study group (UK): Gerry Rayman (Group lead, The Ipswich Hospital NHS Trust), Rajesh Rajendran (The Ipswich Hospital NHS Trust), Chris Kerry (The Ipswich Hospital NHS Trust), Ainslie Lang (Royal United Hospital Bath NHS Trust), James Young (Worcestershire Acute Hospitals NHS

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Table 1:

Variable		Each individual Trust data											Combined data across all Trusts
		1	2	3	4	5	6	7	8	9	10	11	
Number of beds*		537	690	344	264	449	939	680	997	274	690	293	6157
Diabetes Inpatient Specialist Nurse time devoted to inpatient diabetes care†		75.5	97	30	20	20	78	75	52	10	32	48.5	538
Number of 'at risk' subjects	All	85	82	40	43	67	156	73	155	50	74	41	866
	Insulin	50	56	26	18	39	103	44	96	29	52	28	541
	Sulphonylurea	32	25	12	22	24	44	22	52	18	20	12	283
	Both‡	3	1	2	3	4	9	7	7	3	2	1	42
Number of hypoglycaemic readings	All	334	163	136	115	264	432	234	316	159	198	170	2521
	Insulin	219	107	90	61	161	257	161	199	96	118	125	1594
	Sulphonylurea	105	55	34	51	89	154	61	104	46	68	34	801
	Both‡	10	1	12	3	14	21	12	13	17	12	11	126
	Mild hypoglycaemia	239	124	86	81	177	309	165	203	103	134	108	1729
	Severe hypoglycaemia	95	39	50	34	87	123	69	113	56	64	62	792
Hypoglycaemia per 100 bed ratio§	All	62.2	23.6	39.5	43.6	58.8	46	34.4	31.7	58	28.7	58	41
	Mild hypoglycaemia	44.5	18	25	30.7	39.4	32.9	24.3	20.4	37.6	19.4	36.9	28.1
	Severe hypoglycaemia	17.7	5.6	14.5	12.9	19.4	13.1	10.1	11.3	20.4	9.3	21.1	12.9
Hypoglycaemic readings per subject	Median	2	1	2	2	3	2	2	2	2	1	2	2
	Mean	3.93	1.99	3.4	2.7	3.94	2.77	3.21	2.04	3.18	2.68	4.15	2.91
	Range	1-29	1-9	1-11	1-23	1-18	1-16	1-13	1-11	1-12	1-14	1-30	1-30
Subjects with ≥5 readings of hypoglycaemia during the study period		20	7	10	5	18	27	15	15	11	15	11	154
Frequency of glucose monitoring	Insulin	BD-QDS	QDS and 3am	QDS	QDS	BD-QDS	QDS	QDS	QDS	QDS	QDS	QDS	-
	Sulphonylurea	BD-QDS	QDS and 3am	BD-QDS	BD	BD-QDS	BD-QDS	QDS	BD-QDS	QDS	OD-QDS	QDS	-
Hospital meal timings	Breakfast	7:30	7:00	7:00 - 8:00	8:30	7:30 - 8:30	7:00 - 9:00	7:30 - 8:30	7:45 - 8:30	7:45 - 8:30	7:00 - 8:00	8:00	-
	Afternoon meal	12:00	12:00	12:00-13:00	12:15	12:00-13:00	12:00-14:00	11:30-12:45	12:00-13:00	12:00-13:00	12:00-13:00	12:00	-
	Evening meal	17:00	17:00	18:00-19:00	17:00	17:00-18:00	17:00-19:00	16:30-17:45	17:00-18:00	17:00-18:00	17:00-18:00	17:00	-
Time period of hypoglycaemic readings													
Daytime	09:00-14:59	75	30	25	8	33	61	45	46	25	14	31	393
	15:00-20:59	50	33	29	25	51	78	46	65	24	41	47	489
	09:00-20:59	125	63	54	33	84	139	91	111	49	55	78	882
Night-time	21:00-02:59	93	36	36	34	69	133	68	76	45	51	45	686
	03:00-08:59	116	64	46	48	111	160	75	129	65	92	47	953
	21:00-08:59	209	100	82	82	180	293	143	205	110	143	92	1639
Percentage of night-time hypoglycaemia		62.6	61.3	60.3	71.3	68.2	67.8	61.1	64.9	69.2	72.2	54.1	65

*Bed numbers exclude paediatric, maternity and day case units

†Average Diabetes Inpatient Specialist Nurse time (hours per week) devoted to inpatient diabetes care

‡Subjects on both insulin and sulphonylurea therapy

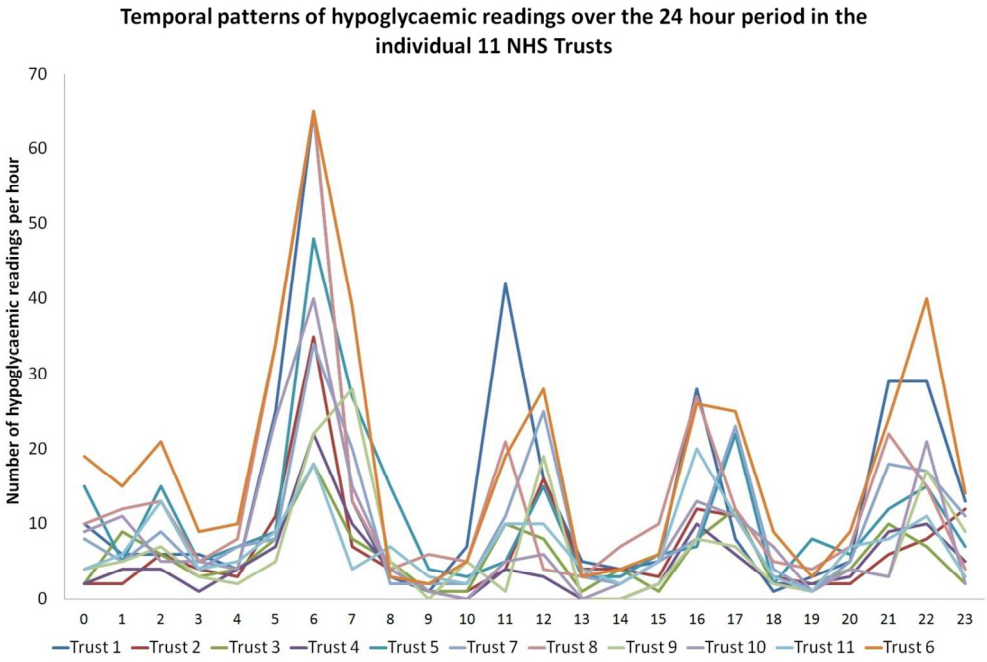
§Calculated as 100 * number of hypoglycaemic readings ÷ number of beds

No Trust guaranteed the provision of a bedtime snack for inpatients with diabetes

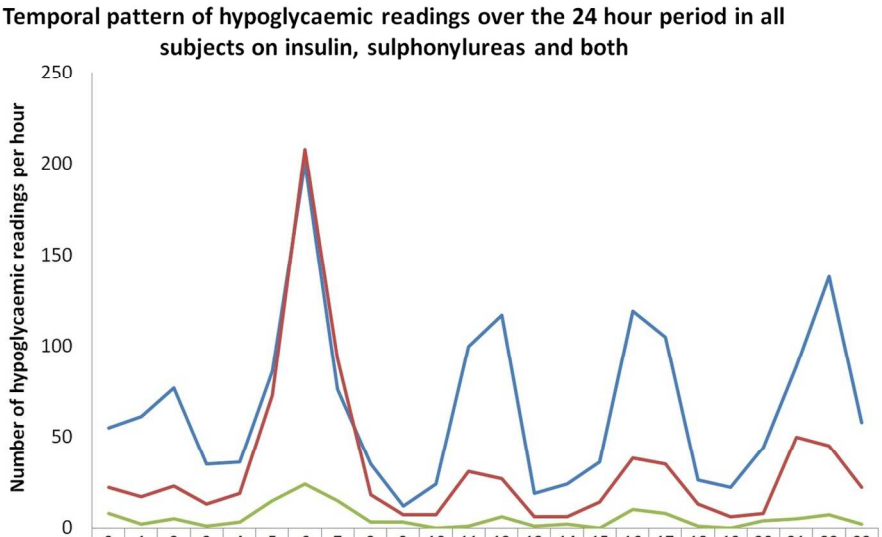
Table 2:

Variable		All	Insulin	Sulphonylurea	Both Insulin and Sulphonylureas
Number of subjects		866	541	283	42
Number of hypoglycaemic readings (%)	All	2521	1594	801	126
	Severe hypoglycaemia	792 (31.4)	572 (35.9)	180 (22.5)	40 (31.7)
	Mild hypoglycaemia	1729 (68.6)	1022 (64.1)	621 (77.5)	86 (68.3)
Subjects with ≥5 readings of hypoglycaemia per subject during the study period (%)		154 (17.8)	96 (17.7)	49 (17.3)	9 (21.4)
			p=0.923		
Number of hypoglycaemic readings per subject	Mean±SD (Range)	2.91±3.16 (1-30)	2.95±3.29 (1-30)	2.83±2.89 (1-29)	3±3.21 (1-12)
	Median (Interquartile range)	2 (1-3)	2 (1-3)	2 (1-4)	1 (1-3.25)
			p=0.888		
Age (years)	Mean±SD (Range)	71±16 (18-98)	67±18 (18-97)	76±10 (42-98)	75±9 (46-91)
	Median (Interquartile range)	75 (64-82)	73 (56-81)	78 (70-83)	77 (69-81)
			p=0.0001		
HbA1c in mmol/mol (%)	Mean [Range]	n=575*	n=364*	n=181*	n=30*
		69(8.5) [28(4.7)-177(18.3)]	73(8.8) [28(4.7)-177(18.3)]	60(7.6) [33(5.2)-161(16.9)]	73(8.8) [46(6.4)-115(12.7)]
	Median [Interquartile range]	64(8) [53(7)-80(9.5)]	69(8.5) [56(7.3)-83(9.7)]	56(7.3) (47(6.5)-66(8.2)]	73(8.8) [55(7.2)-86(10)]
			p=0.0001		
Length of stay (days)	Mean±SD (Range)	n=862*	n=540*	n=282*	n=40*
		17±17.1 (1-101)	16.1±17 (1-101)	17±16.2 (1-100)	25±21.9 (1-82)
	Median (Interquartile range)	11 (5-22)	10 (4-21)	11 (6-23)	20 (7-45)
			p=0.098		
Temporal pattern of hypoglycaemic readings					
Daytime hypoglycaemia	09:00-14:59	393	296	84	13
	15:00-20:59	489	352	114	23
	Total 09:00-20:59	882	648	198	36
Night-time hypoglycaemia (%)	21:00-02:59	686	478	179	29
	03:00-08:59	953	468	424	61
	Total 21:00-08:59	1639 (65)	946 (59.3)	603 (75.3)	90 (71.4)
			p=0.0001		

*Subjects in whom data available



Temporal patterns of hypoglycaemic readings over the 24 hour period in the individual 11 NHS Trusts. The x axis represent the time period, for e.g. 0 represents the time period between 00:00 and 00:59 hours, 1 represents the time period between 01:00 and 01:59 hours etc. The y axis represents the number of hypoglycaemic readings occurring in that time period. The figure demonstrates very similar temporal patterns for all Trusts.
133x90mm (300 x 300 DPI)



	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Insulin (N=1594)	55	61	77	35	36	86	200	76	35	12	24	100	117	19	24	36	119	105	26	22	44	89	138	58
Sulphonylurea (N=801)	22	17	23	13	19	73	208	93	18	7	7	31	27	6	6	14	38	35	13	6	8	50	45	22
Both (N=126)	8	2	5	1	3	15	24	15	3	3	0	1	6	1	2	0	10	8	1	0	4	5	7	2

Temporal patterns of hypoglycaemic readings over the 24 hour period in all subjects on insulin, sulphonylureas and both. The x axis represent the time period, for e.g. 0 represents the time period between 00:00 and 00:59 hours, 1 represents the time period between 01:00 and 01:59 hours etc. The y axis represents the number of hypoglycaemic readings occurring in that time period. The figure demonstrates that the highest frequency occurs between 05:00 to 07:59 hours for both insulin and sulphonylurea therapies.
138x90mm (300 x 300 DPI)