

## Research: Complications

# Severe hypoglycaemia in adults with insulin-treated diabetes: impact on healthcare resources

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### Abstract

**Aims** To assess resource utilization associated with severe hypoglycaemia across three insulin regimens in a large phase 3a clinical programme involving people with Type 1 diabetes treated with basal–bolus insulin, people with Type 2 diabetes treated with multiple daily injections and people with Type 2 diabetes treated with basal–oral therapy.

**Methods** Data relating to severe hypoglycaemia events (defined as episodes requiring external assistance) from the insulin degludec and insulin degludec/insulin aspart programme (15 trials) were analysed using descriptive statistics. Comparators included insulin glargine, biphasic insulin aspart, insulin detemir and sitagliptin. Mealtime insulin aspart was used in some regimens. This analysis used the serious adverse events records, which documented the use of ambulance/emergency teams, a hospital/emergency room visit  $\leq 24$  h, or a hospital visit  $> 24$  h.

**Results** In total, 536 severe hypoglycaemia events were analysed, of which 157 (29.3%) involved an ambulance/emergency team, 64 (11.9%) led to hospital/emergency room attendance of  $\leq 24$  h and 36 (6.7%) required hospital admission ( $> 24$  h). Although there were fewer events in people with Type 2 diabetes compared with Type 1 diabetes, once a severe episode occurred, the tendency to utilize healthcare resources was higher in Type 2 diabetes vs. Type 1 diabetes. A higher proportion (47.6%) in the basal–oral therapy group required hospital treatment for  $> 24$  h versus the Type 1 diabetes (5.0%) and Type 2 diabetes multiple daily injections (5.3%) groups.

**Conclusion** This analysis suggests that severe hypoglycaemia events often result in emergency/ambulance calls and hospital treatment, incurring a substantial health economic burden, and were associated with all insulin regimens.

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### Introduction

Hypoglycaemia is a major side effect of some glucose-lowering therapies, in particular, insulin and the insulin secretagogues (sulphonylureas and glinides). It is a frequent occurrence in people treated with insulin and is more common in Type 1 than in Type 2 diabetes [1–3]. Hypoglycaemia increases in frequency and severity with the duration of insulin treatment [3]. Impaired awareness of hypoglycaemia is common in people treated with insulin, particularly those with Type 1 diabetes [4].

Hypoglycaemia has a significant burden as it can engender fear and anxiety, disrupt sleep and adversely affect domestic and social life [5,6]. Interestingly, rates of severe hypoglycaemia

have not generally diminished over the years, despite the introduction of insulin analogues and advances in glucose monitoring [7,8]. This may be a consequence of the drive to tighter glucose targets, which have diminished the benefits of technological advances. Attempting to reduce this burden can encourage the maintenance of a suboptimal glycaemic control [5,9,10], and both the severity and frequency of hypoglycaemia unequivocally reduce health-related quality of life [11–14]. Hypoglycaemia is also a burden on healthcare resources and on society as a consequence of the direct costs of its treatment and the indirect costs associated with lost productivity [9,15,16]. These and other factors can negatively influence physicians and people with diabetes, promoting reluctance to initiate or intensify therapy — insulin in particular — because of the perceived burden of hypoglycaemia [10,17].

The benefits of stricter glycaemic control are counterbalanced by the enhanced risk of concomitant hypoglycaemia. The most expensive aspect of treating severe hypoglycaemia

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**What's new?**

- The study is unique in reporting resource use associated with severe hypoglycaemia from a randomized controlled trial setting, because resource use has previously been analysed by using registers in which only the events with resource use have been registered, or by patient questionnaires.
- Severe hypoglycaemia events with and without resource use have been collected from a large-scale clinical trial programme.
- The findings suggest that severe hypoglycaemia often necessitates the use of emergency/ambulance teams and hospital treatment, incurring a substantial healthcare burden, regardless of the type of insulin regimen used.

is hospital admission and inpatient care [15,16]. Severe hypoglycaemia is a common cause of hospitalization in elderly people with diabetes [18–21]. To our knowledge, no large-scale studies of the resource use associated with severe hypoglycaemia have been performed that have examined this resource use according to type of diabetes and insulin regimen. The aim of this analysis was to estimate the resource use attributable to severe hypoglycaemia events in a large cohort of people with insulin-treated diabetes, using data from a large-scale clinical trial programme.

**Materials and methods**

This analysis used data from the insulin degludec (IDeg) and insulin degludec/insulin aspart (IDegAsp) phase 3a clinical trial programme, including 15 phase 3a therapeutic confirmatory trials, which involved more than 8000 participants. All trials were registered on ClinicalTrials.gov, the trial protocols were approved by independent ethics committees or institutional review boards, and written informed consent was obtained from participants before enrolment. Trials were undertaken in accordance with the Declaration of Helsinki and good clinical practice guidelines [22,23]. The trials were categorized into three groups, depending on the patient population and the type of insulin regimen: Type 1 diabetes receiving basal–bolus therapy, Type 2 diabetes receiving multiple daily injections and Type 2 diabetes receiving basal–oral therapy.

Severe hypoglycaemia events were identified using information relating to adverse-event case reports in the clinical trial safety database. Only clearly stated resource use was included in the analysis, and all events were analysed independently. The data were analysed descriptively, taking into consideration three variables (that are not necessarily mutually exclusive):

1. Non-medical assistance only, with the response categories: Yes, No.

2. Ambulance or (onsite) emergency team, with the response categories: Yes, No.

3. Hospital or emergency room visit, with the response categories: No, Yes  $\leq$  24 h, Yes  $>$  24 h.

Given the multiplicity of countries in the trial programme, it was decided not to attempt to distinguish between hospital inpatient treatment and emergency room treatment (with subsequent discharge), because the local procedures varied. Hospital visits were therefore distinguished solely on duration ( $\leq$  24 h or  $>$  24 h).

**Results**

Details of the trials and characteristics of the patient populations are summarized in Table 1 [24–36]. In general, people with Type 1 diabetes had a lower mean age, longer disease duration and lower BMI compared with those with Type 2 diabetes. Across the 15 open-label, randomized, treat-to-target clinical trials, severe hypoglycaemia was an infrequent occurrence: 536 severe hypoglycaemia events were recorded and analysed from a total of 8364 patient records. Most occurred in people with Type 1 diabetes receiving basal–bolus therapy, fewer occurred in those with Type 2 diabetes on multiple daily injections, and a small number occurred in people with Type 2 diabetes on basal–oral therapy (Table 1). One reported event of severe hypoglycaemia had a fatal outcome.

Overall, 157/536 (29.3%) of severe hypoglycaemia events required an ambulance/emergency team (mainly involving paramedics, but also including physicians, although the analysis did not distinguish between them) (Table 2). Additionally, following 100/536 (18.7%) of the severe hypoglycaemia events, hospital or emergency room treatment was required, with 36/536 (6.7% points) of these requiring a hospital stay of  $>$  24 h (Table 2).

Although fewer events were recorded in people with Type 2 compared with Type 1 diabetes, once an event occurred, the proportion resulting in hospital or emergency room treatment was greatest in the basal–oral therapy treatment group. Resources were used in relation to 57.1%, 45.3% and 37.9% of severe hypoglycaemia events in the Type 2 diabetes basal–oral therapy, Type 2 diabetes multiple daily injections and Type 1 diabetes basal–bolus groups, respectively (Fig. 1). The greatest difference was in the proportion of events requiring a hospital stay of  $>$  24 h: 47.6% in the Type 2 diabetes basal–oral therapy, 5.3% for Type 2 diabetes multiple daily injections, and 5.0% for the Type 1 diabetes basal–bolus group (Table 2).

**Discussion**

Poor glycaemic control in diabetes is associated with serious complications such as sight-threatening retinopathy and renal failure, and optimizing glycaemic control is fundamen-

**Table 1** Severe hypoglycaemia events by trial

Group	Trial type	Trial	Number of subjects randomized	Duration of trial (weeks)	Number of events	Proportion of patients with events <sup>†</sup>	Rate per 100 patient years of exposure	Age, years mean (SD)	Duration of diabetes, years, mean (SD)	BMI, kg/m <sup>2</sup> , mean (SD)
Type 1 diabetes basal-bolus	IDeg vs. IGlAr trials	BEGIN Basal-bolus Type 1 (3583) [24]	629	52	113	11.8%	20	43.0 (13.6)	18.9 (12.0)	26.3 (3.8)
		BEGIN Flex T1 (3770) [25]	493	26	90	11.0%	40	43.7 (13.1)	18.5 (12.2)	26.7 (3.9)
		BEGIN BB T1 (3585) [26]	456	26	73	10.6%	34	41.3 (14.7)	13.9 (10.3)	23.9 (3.5)
		BOOST T1 (3594, inc. extension 3645) [27]	548	52	144	14.9%	33	41.3 (13.2)	17.4 (11.6)	26.4 (4.0)
Type 2 diabetes multiple daily injections	IDeg vs. IGlAr trial	BEGIN Basal-bolus Type 2 (3582) [28]	1006	52	53	4.5%	6	58.9 (9.3)	13.5 (7.3)	32.2 (4.6)
		BOOST Intensify Premix I (3592) [29]	447	26	34	5.2%	17	58.7 (9.8)	13.0 (7.1)	29.3 (4.8)
		BOOST Intensify All (3597) [30]	424	26	8	1.4%	4	59.8 (10.0)	16.3 (8.0)	25.4 (3.5)
		BEGIN Low Volume (3672) [31]	460	26	0	0.0%	0	57.5 (9.2)	8.2 (6.2)	32.4 (5.4)
Type 2 diabetes basal-oral therapy	IDeg vs. IGlAr trials	BEGIN Once Long (3579) [32]	1030	52	7	0.7%	1	59.1 (9.8)	9.2 (6.2)	31.1 (4.7)
		BEGIN Once Asia (3586) [33]	435	26	1	0.2%	0	58.6 (9.9)	11.6 (6.5)	25.0 (3.6)
		BEGIN Flex (3668) [34]	687	26	6	0.7%	2	56.4 (9.6)	10.6 (6.7)	29.6 (4.7)
		BEGIN Early (3580) (in IDeg arm) [35]	458	26	1	0.2%	1	55.7 (10.9)	7.7 (6.0)	30.4 (5.1)
Type 2 diabetes basal-oral therapy	IDeg vs. sitagliptin trial	BOOST Start 1 (3590)**	530	26	2	0.4%	1	56.9 (9.1)	9.2 (6.1)	30.7 (5.1)
		BOOST Intensify Basal (3593)**	465	26	4	0.6%	2	58.1 (9.8)	11.5 (7.0)	30.1 (5.2)
		BOOST Japan (3896) [36]	296	26	0	0.0%	0	60.5 (9.8)	11.7 (8.0)	25.1 (3.8)

NB. The three-times-weekly trials were not included in this analysis.

\*All but one event occurred in the IGlAr arm in the trials 3590 and 3593.

<sup>†</sup>As a proportion of the number of randomized patients included in the safety analysis set in each trial. All trial products were administered once daily unless otherwise stated.

<sup>‡</sup>Study not published.

BIAsp 30, biphasic insulin aspart; BID, twice daily; BMI, body mass index; IDeg, insulin degludec; IDegAsp, insulin degludec/insulin aspart; IDet, insulin detemir; IGlAr, insulin glargine.

**Table 2** Proportion of severe hypoglycaemia events leading to ambulance, emergency room or hospital visits

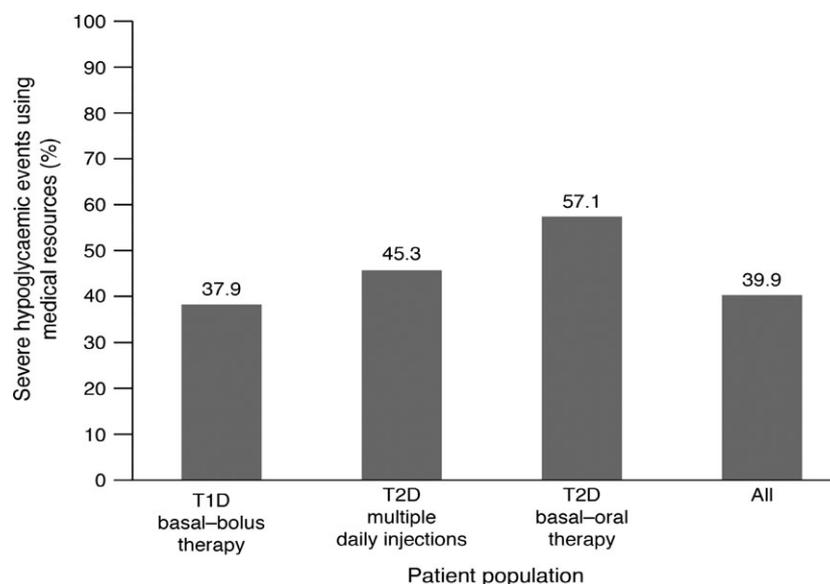
Group	Total number of events	Resource use	Number of events (%)
Type 1 diabetes basal–bolus	420	Non-medical assistance only	261 (62.1)
		Ambulance/emergency team	130 (31.0)
		Hospital or emergency room ≤ 24 h	40 (9.5)
		Hospital > 24 h	21 (5.0)
Type 2 diabetes multiple daily injections	95	Non-medical assistance only	52 (54.7)
		Ambulance/emergency team	24 (25.3)
		Hospital or emergency room ≤ 24 h	22 (23.2)
		Hospital > 24 h	5 (5.3)
Type 2 diabetes basal–oral therapy	21	Non-medical assistance only	9 (42.9)
		Ambulance/emergency team	3 (14.3)
		Hospital or emergency room ≤ 24 h	2 (9.5)
		Hospital > 24 h	10 (47.6)
All	536	Non-medical assistance only	322 (60.1)
		Ambulance/emergency team	157 (29.3)
		Hospital or emergency room ≤ 24 h	64 (11.9)
		Hospital > 24 h	36 (6.7)

tal to minimize this morbidity [37–39]. However, severe hypoglycaemia, a serious adverse effect of some glucose-lowering therapies — particularly insulin — can also cause significant morbidity and have quality of life and economic consequences.

This analysis utilized data from a large-scale clinical trial programme and subdivided records by type of diabetes and also by insulin regimen. This has shown that in the controlled clinical trial setting, severe hypoglycaemia seldom occurs, but when it does, it leads to direct healthcare resource use in ~ 40% of cases.

A large difference was observed between the different regimens in the proportion of people experiencing severe

hypoglycaemia who required hospitalization for > 24 h. The proportion of participants using resources following a severe hypoglycaemia event was highest in the people with Type 2 diabetes on basal–oral therapy, despite the overall lower number of events compared with the patients on multiple daily injections. This may be because many of the participants receiving basal–oral therapy (and their family/carers) were much less experienced in treating severe hypoglycaemia. They may be more inclined to seek medical assistance, in contrast to people with Type 1 diabetes and those with insulin-treated Type 2 diabetes taking multiple daily injections who probably have greater experience of exposure to severe hypoglycaemia. People with diabetes and their family



**FIGURE 1** The proportion of severe hypoglycaemia events utilizing medical resources. Medical resource use includes use of ambulance/emergency team, hospital visit < 24 h and > 24 h. The variables measured were not necessarily mutually exclusive. T1D, Type 1 diabetes; T2D, Type 2 diabetes.

members in these groups are less likely to seek assistance because they have learned to cope effectively with this emergency and the immediate requirements of treating an episode of severe hypoglycaemia. Furthermore, the people with Type 2 diabetes included in the trials had a higher mean age than those with Type 1 diabetes, and this may mean that more of them had more comorbidities, were frailer and were more vulnerable to morbidity associated with severe hypoglycaemia, so contributing to the longer duration of hospital admissions. Several studies have shown that hypoglycaemia requiring hospital treatment is more frequent in the elderly compared with younger people with diabetes [19–21].

It should also be noted that, in some trials, people with Type 2 diabetes were taking concomitant oral anti-diabetes agents, including sulphonylureas, and it is not clear whether these contributed to any of the severe hypoglycaemia events. Some specialists believe that hospital admission is necessary for people who experience severe hypoglycaemia as a consequence of sulphonylurea therapy, which might account for some of the hospital attendances by the participants receiving basal–oral therapy [40,41]. A previous study observed that the proportion of people for whom emergency medical assistance was sought was higher in those with Type 2 diabetes than with Type 1 diabetes (33% vs. 10%) [2]. A population-based study analysing resource use associated with severe hypoglycaemia treated by emergency medical services in Tayside, Scotland, recorded 260 episodes over a 12-month period. Of these, 34% involved the ambulance service alone, 7% were treated by emergency/primary care services alone and 52% used both. Some 28% of cases required hospital admission, resulting in hospital occupancy of 230 bed days [16]. Although this is higher than the 18.6% who visited hospital in our study, it should be noted that this Scottish study analysed only those events that had required emergency medical treatment, thus representing a more severe end of the spectrum.

The use of medical resources following severe hypoglycaemia is costly, considering the large number of people with insulin-treated diabetes and the extensive use of sulphonylureas. For example, an estimate of this resource utilization and associated financial burden based on the 2013–2014 UK National Health Service tariffs for ‘Admitted Patient Care & Outpatient Procedures — Diabetes with Hypoglycaemic Disorders’ equates to £1269 for people aged  $\leq 69$  years and £2187 for people aged  $\geq 70$  years, in addition to £235 for an ambulance transfer. This yields an average cost per event across treatment regimens of £305 [(11.9% + 6.7%) \* £1269 + 29.3% \* £235] for people aged  $\leq 69$  years and £476 [(11.9% + 6.7%) \* £2187 + 29.3% \* £235] for people aged  $\geq 70$  years [42]. Hypoglycaemia is more costly in elderly populations with diabetes, who may be much more susceptible to severe hypoglycaemia, perhaps in relation to co-existing comorbidities [18–21].

Several other studies using different methodologies have provided results that are in broad agreement with our study.

Hospitalization is the major cost associated with treating hypoglycaemia, but costs vary depending on the countries involved and local practices and procedures. For example, the costs associated with treating hypoglycaemia in Germany are higher than elsewhere because people with diabetes are often admitted to hospital for several days to receive additional education [43]. The study based in Tayside estimated the direct costs of treating severe hypoglycaemia — based on £127 for an ambulance, £89 for emergency room treatment and £218 for each patient admitted to a ward — to be over £13 million per year for the UK in 2003 (equivalent to £17 million in 2014 prices) [16]. Based on these values, the cost of a single severe hypoglycaemia event, which required some medical assistance, has been estimated at £335 [44]. Data obtained using a questionnaire regarding a participant’s most recent severe hypoglycaemia event performed in Germany, Spain and the UK revealed that the cost of treating a person with Type 2 diabetes (Germany, €533; Spain, €691; UK, €537) was higher than for a person with Type 1 diabetes (€441, €577 and €236, respectively) [15]. A US-based study investigating the cost of hypoglycaemia in people with insulin-treated Type 2 diabetes estimated the direct costs of severe events requiring assistance from a healthcare professional as \$1729, whereas those events requiring non-medical assistance were \$242 per event [45].

Most previous studies have been retrospective assessments of all people with severe hypoglycaemia, and often exclusively those who had utilized additional healthcare resources. Therefore, they have not consistently stratified people according to their treatment regimen. Although some of these studies included cost analyses, they did not include all severe hypoglycaemia events, so it is difficult to determine what proportion of events required ambulance and hospital treatment. This study benefits from its size and the more accurate and reliable recording associated with controlled clinical trials, by contrast with data that have been collected in real-world observational or retrospective studies.

This study has the limitation that the rates of hypoglycaemia may be lower than in a real-world setting, because people at high risk of severe hypoglycaemia or who were judged by the investigator to have impaired hypoglycaemia awareness were excluded from the clinical trials. However, because the examination was not primarily aimed at assessing the risk of events, but rather exploring the consequences of such an event, it is unclear to what extent such a limitation would influence the results. Additionally, because of the global nature of the clinical trials, a huge variation in healthcare utilization and local procedures are to be expected, making estimates of resource use difficult to determine with accuracy. Healthcare utilization in trials is often protocol driven, but this has not been assumed in this analysis because of the acute nature of severe hypoglycaemia. Potential exists for the under-reporting of ambulance use, or inconsistent reporting of resource use. Although it is known when people had attended hospital, information about how

they arrived there was not consistently recorded, so only clearly stated resource use was included in the analysis. This study did not attempt to capture length of stay or what medication was received because this would be healthcare-sector specific and could be confounded by other comorbidities. The study has reported only the direct resource use relating to the involvement of emergency services and hospital treatment and does not include additional blood glucose measurements, costs of glucagon or intravenous dextrose, or any subsequent medical consultations that were necessary following a severe hypoglycaemia episode. These costs were estimated in a Canadian study [46]. Productivity loss or the costs of informal caregivers were not measured.

## Conclusion

This analysis suggests that severe hypoglycaemia events often result in emergency/ambulance calls and treatment in hospital, thereby incurring a substantial economic burden. A high rate of resource utilization was observed with all insulin regimens, and although the incidence of severe hypoglycaemia events was low, the greatest level of resource use following an event occurred in people with Type 2 diabetes on a regimen of basal insulin combined with oral anti-diabetes drugs.

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The clinical trials were sponsored by Novo Nordisk. Novo Nordisk contributed to the study design and conduct, data collection, analysis and interpretation of the trials.

## Competing interests

SH has served on advisory panels and speaker bureaus for Eli Lilly, Novo Nordisk and Takeda, and received research support from Medtronic. BMF has served on advisory panels and speaker bureaus for Eli Lilly, Novo Nordisk, MSD, Sanofi, Boehringer Ingelheim and Janssen. MH and JG are employees of Novo Nordisk. SG has served on advisory boards for Novo Nordisk, Sanofi, Takeda and Eli Lilly and has received research support from Novo Nordisk, Sanofi and Takeda.

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## Authors' contributions

All authors contributed to the design, interpretation, writing, evaluation and approval of this manuscript. JG and MH

were responsible for the data collection and analysis. SH takes responsibility for the integrity of this article.

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