The clinical impact of hypoglycemia in hospitalized patients

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ABSTRACT

Hypoglycemia is a very common problem, mostly in frail, severely ill, older hospitalized patients. Hypoglycemia has been implicated in the development of adverse clinical outcomes, including an increased mortality. Fear of iatrogenic hypoglycemia remains an obstacle to adequate inpatient glycemic control. It may be considered as a marker of disease, rather than cause in itself of undesirable events. Several factors, such as treatment with exogenous insulin, mismatch between insulin administration and meal intake with the loss of normal counter regulatory responses, place patients with diabetes at higher risk for hypoglycemia than the ones without diabetes. In this review we discuss the causes and predictors of hypoglycemia in non-critically ill hospitalized patients and how to prevent them. Subcutaneous insulin with basal-bolus regimen rather than sliding scale and the use of analogues may minimize hypoglycemic events. In-patient glycemic management should be patient-centered, following the current guidelines, and aimed to prevent hypoglycemic events.

Introduction

The achievement and maintenance of a state of normal blood glucose in hospitalized patients is crucial, owing to the fact that both hypog and hyperglycemia can be extremely dangerous. It has been clearly shown that hyperglycemia is associated with an increase in mortality and in-hospital complications. Initial small trials have shown that aggressive control of blood glucose with intensive insulin therapy could improve the prognosis of these patients, but subsequent trial, carried out on a larger scale, reported a higher incidence of hypoglycemia in patients in intensive treatment, resulting in a worse prognosis. This evidence resulted in defining protocols of treatment of hyperglycemia in hospitalized patients, in which a reasonable and acceptable glycemic control is defined as a blood glucose varying between 99 and 180 mg/dL for the most part of patients. If we take into account that in the United States in 2010 were discharged approximately 8.3 million people with a diagnosis of diabetes, i.e. 21.3% of all patients discharged, we understand the extent of the problem and its clinical importance. Hypoglycemia causes acute events, potentially fatal; therefore it remains a major obstacle to the optimal glycemic treatment in the hospitalized patient. It is now well understood that patients with both spontaneous and iatrogenic hypoglycemia are at a high risk of complications and mortality, as well as of a greater length of hospital stay. Although this association is now well-established, yet it is not clearly documented a direct causality. In this review we will try to examine the causes of hypoglycemia in patients hospitalized in the Internal Medicine Departments and the importance of preventing such events by means of appropriate therapeutic strategies.

Definition and prevalence of hypoglycemia

A blood sugar level below 70 mg/dL is the threshold generally used to indicate hypoglycemia. The true hypoglycemia is defined by the activation of counter-regulatory mechanisms and this varies from individual to individual. The release of epinephrine and glucagon occurs at blood glucose levels close to 70 mg/dL, followed by the release of somatotropin and cortisol when the blood sugar level goes down to 60 mg/dL. The onset of autonomic symptoms requires lower blood glucose levels, usually around 50 mg/dL. It has been defined by the term severe hypoglycemia low blood sugar lower than 50 mg/dL or requiring the assistance of another person. Using in patients hospitalized the counter regulation thresholds, derived from studies conducted in
outpatients, could be problematic, as the former may have an impaired counter-regulation.\(^8\,^9\) In addition, hospital patients may exhibit only neuroglycopenic signs, without any preceding autonomic symptoms. This is due to many factors including the polypharmacy, multi-organ dysfunction and the presence of long lasting diabetes, all factors usually present in the internal medicine patient.\(^10\) Therefore, to define a hypoglycemia in hospitalized patients, rather than using the glucose counter-regulation thresholds or the development of symptoms, it is recommended to safely cut off \(<70\,\text{mg/dL},\) a value recently adopted by two major American scientific societies.\(^11\)

Owing to variations in defining of hypoglycemia, it is not surprising that the estimation of its prevalence in hospitalized patients shows large fluctuations, ranging from 3% to 30%. Many studies, moreover, do not distinguish between patients with and without diabetes, nor among those critically ill - admitted in Intensive Care Units (ICU) compared to not critical patients. Among the people with and without diabetes admitted to an internal medicine ward, the incidence of hypoglycemia (defined as blood glucose \(<70\,\text{mg/dL}\)) varies between 3.5% and 10.5%.\(^12\) Just in patients with diabetes, however, hypoglycemia may occur in 12%-18% of cases, or highest percentage if treated with more aggressive glucose-lowering therapy.\(^13\) In a retrospective review, among more than 4000 admissions in Internal Medicine Department, hypoglycemia was found in 8% of hospitalizations and in 3% of patients admitted.\(^14\) In a study including data from 575 hospitals, hypoglycemia (blood glucose \(<70\,\text{mg/dL}\)) occurred in 6.3% of patients admitted to the ICU and in 5.7% of patients in normal wards.\(^15\) In several intervention studies performed on patients admitted in ICU higher incidences of hypoglycemia were observed, with values ranging from 5% to 18% in the intensive treatment group.\(^1,^4,^6\)

**Risk factors of hypoglycemia**

Factors contributing to hypoglycemic events in hospitalized patient may be multiple (Table 1). Although diabetes and the subsequent use of hypoglycemic drugs is the most common risk factor, only 50% of hypoglycemic events occurs in diabetic patients or in those receiving insulin.\(^17,^18\) The spontaneous hypoglycemia, which occurs without any clear precipitating cause, must be distinguished from that one drug-induced, even as it has a poor prognosis and a different pathogenesis. Risk factors for spontaneous hypoglycemia are septic shock, comorbidities (as defined by the Charlson comorbidity index), drug interactions in polypharmacy, renal failure, liver or adrenal disease, severe heart failure and neoplasms.\(^17,^18\) We have always to remember that during hospitalization, patients undergo changes of their insulin sensitivity and counter-regulatory hormone, secondary to the disease, procedures and treatment carried out.\(^19,^20\) Older patients also have often organ dysfunction age related, which alters insulin sensitivity and drug metabolism, resulting in the enhancement of hypoglycemic events.\(^10\) Elderly people show symptoms of hypoglycemia at a considerably lower glycemic threshold compared to the young (54\(\pm3.6\,\text{mg/dL}\) vs 65\(\pm1.8\,\text{mg/dL}\))\(^9\) and frequently for their altered mental conditions are not able to communicate their symptoms. In diabetic patients, the most obvious risk factor for hypoglycemia is the exogenous administration of insulin or the stimulation of insulin secretion by secretagogues containing drugs. In these cases, since that hyperinsulinemia is drug-induced and non-physiological, the levels of insulin will not reduce in response to the lowering of blood sugar. You have also to take into account that the hormonal counter-regulatory response to hypoglycemia is often impaired in patients with diabetes (especially of type 1 and with long duration of diabetes), which have a reduced secretory response to glucagon and epinephrine. Another important factor to consider is that previous recurrent hypoglycemias facilitate further hypoglycemic episodes, since the threshold for counter-regulatory response increases when blood sugar levels are high, while it decreases in the case of normal values.\(^21\) Therefore, a single episode of hypoglycemia increases the risk of subsequent episodes, thus triggering a vicious cycle of recurrent hypoglycemia. This phenomenon is well documented on the inpatient treatment. One study reported that 40% of hospitalized patients had recurrent episodes of hypoglycemia,\(^22\) while in another study severe hypoglycemic episodes were preceded by mild hypoglycemia in more than 60% of cases.\(^23\) Another factor favoring a dysregulation of the counter is the

<table>
<thead>
<tr>
<th>Risk Factors of Hypoglycemia</th>
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<tr>
<td><strong>Iatrogenic</strong></td>
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<tr>
<td>• Too aggressive treatment protocols</td>
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<td>• Poor coordination between the temporal administration of insulin and meals</td>
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<td>• Unscheduled suspension in eating</td>
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<td>• Interruption of steroid therapy without relating changes in insulin</td>
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<td>• Using the sliding scale</td>
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<td><strong>Organic</strong></td>
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<td>• History of frequent hypoglycemia or unawareness hypoglycemia</td>
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<td>• Autonomic neuropathy</td>
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<td>• Advanced age with or without cognitive impairment</td>
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<td>• Sepsis</td>
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<td>• Critical illness</td>
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<td>• Renal or hepatic impairment</td>
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<tr>
<td>• Cancer</td>
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<td>• Adrenal insufficiency</td>
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Table 1. Risk factors for hypoglycemia in hospitalized patients.
presence of autonomic neuropathy. Although there are no studies in hospitalized patients, it is very likely that the diabetic autonomic neuropathy may be a significant risk factor for hypoglycemia in diabetic patients. Insulin therapy is elective in the hospital for blood glucose control. Although its pharmacokinetic profile is very well predictable with respect to non-insulin therapies and its dosage can be very flexible, insulin is one of the high-alert medications in hospitalized patients. The association between hypoglycemia and insulin administration is dose dependent. A retrospective case-control study of 1990 patients with diabetes admitted to hospital showed that the risk of hypoglycemia was doubling with insulin doses between 0.6 and 0.8 U/kg/day, while threefold with insulin doses >0.8 U/kg/day; on the other hand there was no increase in hypoglycemic events at doses of 0.2-0.6 U/kg/day, compared to doses <0.2 U/kg/day. The failure to correct insulin doses in the case of reduced food intake contributes to the increased risk of hypoglycemia. The sudden interruption of enteral or parenteral nutrition is yet another important risk factor, unless another source of glucose is not administered. Any variation of the type of nutrition, without an adequate proportionate change of the doses of insulin, has been shown to be responsible for 82% of hypoglycemic events. Patients who are regularly and at the right times fed may be at risk of hypoglycemia too, without adequate pre-prandial blood glucose monitoring and timing of insulin administration and/or meals control; finally, changes in the content of carbohydrates in the meal is another risk factor in subjects receiving fixed insulin doses with meals. Despite the scientific evidence proved the ineffectiveness and the lack of security of sliding scale insulin (SSI), this is unfortunately still a very common practice in hospital wards. The SSI refers to the practice of administering doses of regular insulin or rapid analogous, depending on blood glucose values at the time. There is a large variability between professionals in establishing at which blood glucose levels to start the SSI and what doses to use. This regimen is usually taken before meals and at bedtime, without taking into consideration if the patient could or not ingest calories at bedtime. Therefore, the use of SSI contributes substantially to hypoglycemias, especially at night. The SSI should instead be understood as a correction or additional insulin in patients who are already running a previously established basal-bolus dose. In these situations, small doses of rapid-acting insulin are administered before meals (in patients who are fed) or every 6 h (in patients who do not eat or in artificial nutrition). Sudden changes in the normal hospital routine, such as the abrupt execution of the procedures that force the patient to skip a meal, the unpredictability of the dietary intake, the interruption of steroid treatment without any changes of glycemic therapy, are all factors contributing to the onset of hypoglycemia. Finally, even in diabetic patients, all those risk factors for spontaneous hypoglycemia listed above, in addition to the risks of insulin therapy, may contribute to the high incidence of hypoglycemic events.

Consequences of hypoglycemia

The consequences of the acute hypoglycemia concern mainly the pro-thrombotic and pro-inflammatory effects. Indeed, in experimental models, hypoglycemia causes an increase in catecholamine levels, inflammatory markers, platelet activation, and endothelial dysfunction. Both in healthy subjects and type 1 diabetes, hypoglycemia results in an increase of monocytes adhesiveness, markers of platelet activation (P-selectin) and inflammation (monocytes CD-40, IL-6 and hrCRP), and of adhesion molecules (VCAM-1, ICAM-1, E-selectin). Some of the pro-thrombotic and pro-inflammatory effects of acute hypoglycemia may be reduced by β-blockers, thereby assuming that these changes are induced through adrenergic activation and therefore that they can be attenuated in individuals with an impaired counter-regulation. There are still no studies demonstrating whether acute hypoglycemia effects may also include patients who, already sick and hospitalized, show in themselves an increase of inflammatory mediators, catecholamines and stress hormones. Hypoglycemia can lead to cardiac complications, especially ischemia and arrhythmias, that were even associated with mortality. Hypoglycemia has been associated with transient electrocardiogram changes during a continuous blood glucose and electrocardiographic monitoring, and to the QT interval lengthening, which may trigger reentrant arrhythmias. These cardiac abnormalities might be responsible for the dead in bed syndrome, i.e. the phenomenon of the sudden death at night, described in young patients with type 1 diabetes. Furthermore, patients with long-term diabetes can develop a cardiovascular autonomic neuropathy, a chronic condition associated with prolongation of the QT interval and an increased risk of sudden death. To date, there are no data demonstrating these cardiovascular alterations in hospitalized patients, since the existing literature relates only to outpatients. There is still a lot of debate on whether hypoglycemia in itself may be the cause of increased cardiovascular events. Indeed, large trials performed in hospitalized patients treated with intensive insulin therapy have reported rare acute cardiac complications, despite frequent and severe hypoglycemias. In the DIGAMI 1 study, in which all patients were hospitalized for acute myocardial infarction (AMI), the arm in intensive insulin therapy had the same incidence of re-infarction, ventricular fibrillation...
and atrio-ventricular conduction disorders, compared to the control arm, despite the fact that 15% of them presented hypoglycemia vs the control group, who had not hypoglycemic events.\textsuperscript{40} Even the EURODIAB Prospective Complications Trial\textsuperscript{42} showed that subjects treated in an intensive way, and thus with a higher incidence of hypoglycemia, did not have an increase in cardiovascular events or of inflammation markers. The lower incidence of hypoglycemia-related cardiac morbidity observed in the trials could be due to the strict patient monitoring, resulting in a short duration of the hypoglycemia. In addition, during hospitalization, the highest concentration of circulating catecholamines, as well as the administration of inotropic drugs, may attenuate the heart rate response to hypoglycemia. Evidence that the daily clinical practice could be quite different, can be inferred from a recent study, carried out by questionnaire, showed how hypoglycemia in hospitalized patients can lead to higher numbers of adverse events, compared to what was so far shown, whereas this is the case for hypoglycemic episodes following the treatment of hyperkalemia.\textsuperscript{43} Hypoglycemia may also cause a variety of neurologic manifestations, ranging from simple irritability to coma. However, cerebral death is very rare and requires a prolonged and severe hypoglycemia. In primates the insulin-induced hypoglycemia can cause brain death when the blood sugar is still below 20 mg/dL for at least 5 h.\textsuperscript{45} Human studies are limited and the best evidence comes from the DCCT/EDIC trial: a careful monitoring of patients in the intensive treatment arm showed that, although the incidence of repeated and severe hypoglycemic episodes, there was no evidence of brain damage.\textsuperscript{44} In patients hospitalized with severe iatrogenic hypoglycemic episodes, hypoglycemia did not only hesitate in neurological deficits, but, on the contrary, was associated with favorable outcomes.\textsuperscript{2} In conclusion, brain death from hypoglycemia, although possible, is very rare in clinical practice. Several studies on hospitalized patients have shown a correlation between hypoglycemia and mortality,\textsuperscript{14,39,45} although the direct liability still remains very uncertain. An observational study proved a kind of J-curve between blood glucose levels and the likelihood of mortality, with lower fatalities with blood glucose levels ranging from 100 to 150 mg/dL.\textsuperscript{46} This associated increased mortality in hospitalized patients may not be caused by hypoglycemia in itself, but may instead be due to the association between hypoglycemic episodes and comorbidities, where hypoglycemic episodes could be a marker of frailty. In hospitalized patients spontaneous hypoglycemia occurs without clear triggering factors, but they are associated with higher mortality compared to iatrogenic hypoglycemas. A retrospective study of a large cohort of patients with or without diabetes, admitted to Departments of Internal Medicine, showed that mortality was higher among patients who had spontaneous hypoglycemas.\textsuperscript{17}

Preventing hypoglycemia

Although the fear of hypoglycemia constitutes a barrier to the optimal glycemic control, subsequent inappropriate treatment of hyperglycemia would be an undesirable approach.\textsuperscript{48} Thus, prevention of hypoglycemic episodes should be achieved through a patient-centered process, able to share appropriate treatment upon the specific nutritional needs of the patient, with proper glucose monitoring, appropriate hospital procedures, and, above all, the capacity to adapt treatment and care, according to the actual clinical needs of our patients (Table 2). The subcutaneous insulin therapy, in accordance to the basal-bolus approach, involves a scheduled administration of therapy, with the long acting insulin approximately represented as 50% of the total daily dose, and the rest administered as rapid-acting insulin, before the three main meals, 20-30% at breakfast, lunch and dinner 30-40%.

Many steps of schemes correction of insulin therapy have been formulated, but the most practical approach seems to be the rule of 1500, for estimating the...
factor of insulin sensitivity. Established the value of insulin sensitivity factor, on the basis of blood glucose data, we can calculate the doses of insulin to administer as a correction factor\(^5\) (Table 3). Thus, the use of this therapeutic approach allows combining doses of insulin-to-insulin sensitivity of the patient, therefore by treating hyperglycemia without any major risk of hypoglycemia. Regarding the calculation of the total dose of insulin in administering the basal-bolus pattern, this varies from 0.2-0.6 U/kg/day, always taking into account the clinical state of the patient. The lower dose (0.2 U/kg/day) may be used to slim patients, or in chronic renal insufficiency or in seniors (older than 70 years); the higher dose can be used in overweight people with acute illnesses (increased insulin resistance) or who are receiving steroids. Of course, the doses of insulin should be amended on the basis of the daily blood glucose monitoring.\(^5\) It is very important to identify patients at risk of hypoglycemic episodes: in these subjects is necessary to implement systems of care by more frequent clinical monitoring, in order to minimize the frequency and the severity of such episodes. Patients with chronic renal failure are a group at high risk for hypoglycemic events. In a study of inpatients with glomerular filtration rate lower than 45 mL/min randomized to a basal-bolus therapy by glargine and glulisine, using two strengths (0.25 or 0.50 U/kg/day), the lower dose group had a slight, but not significant, lower incidence of hypoglycemic episodes compared to the group with the highest dose (15.8% vs 30.0%, \(P=0.08\)), but with no increase in incidence of hyperglycemia. Also in the arm at lower administered doses, hypoglycemic events were present, this strengthening the need for a tight control of blood glucose levels and insulin doses in patients at higher risk of hypoglycemic episodes.\(^5\)\(^1\) For many years there have been developed fast and basal analogues, able, for their own pharmacokinetic profiles, to provide better efficacy and safety. The rapid acting analogues (aspart, lispro or glulisine) lead to some substantial benefits, compared to regular insulin, when used to control postprandial blood glucose values. While regular insulin needs to be injected 30’ before the meals, the rapid acting analogues can be administered immediately before or after a meal, without any change in their action.\(^5\)\(^2\)\(^,\)\(^3\)\(^1\) This is a great advantage in the management of blood glucose levels in the hospital, where often it is not possible to accurately deter-

### Table 2. Prevention of hypoglycemia.

- Avoid using oral hypoglycemic agents
- Carefully consider the clinical status and any risk factors in your patient
- Avoid the use of premixed insulin that do not give a physiological replacement therapy
- Use the analogues, preferably the rapid and basal ones
- Use the correct dose, according to the patient’s sensitivity
- If food intake is not predictable, administer the similar rapid at mid-meal
- Improve blood glucose monitoring
- For patients at higher risk of hypoglycemia use higher glycemic targets
- Implement the use of guidelines and protocols
- Raise \(\beta\) and train in your medical and nursing staff

### Table 3. The calculation of correction bolus based on insulin sensitivity.

<table>
<thead>
<tr>
<th>Blood glucose (mg/dL)</th>
<th>Scale 1</th>
<th>Scale 2</th>
<th>Scale 3</th>
<th>Scale 4</th>
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<tbody>
<tr>
<td>151-200</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>201-250</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>251-300</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>301-350</td>
<td>4</td>
<td>8</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>351-400</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
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</table>

*Insulin sensitivity factor (ISF) is the decrease in blood glucose following administration of 1 U of insulin. ISF is calculated by the rule 1500 (ISF=1500 / TDD), where TDD stands for the total daily dose of insulin (rapid+basal).
mimicking the time or the amount of food that the patient will take. In addition, the peak effect is achieved earlier than with regular insulin, resulting in improved control of postprandial blood glucose, while their shortest duration of action reduces the risk of hypoglycemic episodes later or pre meal. Several clinical trials have shown that the use of rapid acting analogues results in a lower incidence of hypoglycemic events, with the same glycemic control. The physiological basal insulin secretion is mimicked in our diabetic patients by the use of basal or late insulin. The ideal basal insulin should have a 24-h action duration, in absence of peaks. Unfortunately the neutral protamine Hagedorn (NPH) insulin does not absolutely mimic the physiological secretion, since its single administration does not cover the 24 h and its action has a peak toward the second to fourth hour after its administration. These features affect significantly the blood glucose, resulting in potential nocturnal hypoglycemas and hyperglycemia upon awakening. The long-acting basal analogues (glargine and detemir) have solved these problems in a very satisfactory way. Their long duration and their flat profile allow the achievement of good metabolic control, with a significant reduction of night hypoglycemic episodes especially compared to NPH insulin. Basal analogues show even less pharmacokinetic variability, resulting in greater stability blood glucose inter and intra-individual compared to NPH. According to these considerations, the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE)’s statements strongly recommended the use of analogues (glargine and detemir) compared to NPH as insulin baseline. The FADOI-DIAMOND study sub-analysis showed that among diabetic patients admitted to Italian Internal Medicine Units, patients treated with a basal-bolus scheme with analogues have less hypoglycemic episodes compared to those treated with an insulin alone or with a basal sliding scale. In this study was confirmed that hypoglycemia may worse hospital indicators, by a longer hospital stay (12.7±10.9 vs 9.6±6.5 days, P<0.01). In addition, in order to facilitate an adequate glycemic control with the lower possible risk of hypoglycemia, further progress in the field of research of insulin treatment have been defined, by the near future availability, in Italy too, of degludec insulin. This is a new ultra-longacting basal insulin (half-life: about 25 h), which forms soluble multi-hexamers, when injected subcutaneously, determining a deposit from where the degludec insulin is absorbed continuously and slowly in the circulation, leading to a uniform and stable hypoglycemic effect. Degludec insulin shows an intra-patient variability from day to day hypoglycemic effect four times lower in terms of coefficients of variation compared to insulin glargine. Pivotal trials by this new type of insulin showed that in type 1 diabetes, degludec insulin, compared with glargine in a basal-bolus regimen with a rapid acting analogues, with the same glycemic control, resulted in less nocturnal hypoglycemia. In type 2 diabetes, when compared to the glargine in a basal dose regimen only on equal glycemic control, it showed a significant reduction of all 24 h-daily, not only nocturnal, hypoglycemic episodes. These data were well confirmed in elderly subjects too, those aged over 65 years, normally more vulnerable to hypoglycemic episodes. In addition, more than 24 h half-life of this new insulin allows its administration not directly time-dependent, increasing the flexibility of insulin therapy, essential in the management of hyperglycemia in hospitalized patients.

One study evaluated patients with type 2 diabetes, who were divided into three groups: two groups were receiving insulin glargine or degludec (IDeg) every 24 h, while the third received degludec at different times, with a variation in the last administration that ranging from 8 to 40 h; however, over the week, patients always received seven insulin injections, as well as other groups. This study was designed to explore from the point of view of safety and efficacy, the impact of the variability of basal insulin delivery. Results showed that patients in which degludec insulin was administered at variable intervals, at the end of the 26 weeks of treatment reached the same glycemic control, without any increasing risk of hypoglycemia, compared to those in whom the same degludec or glargine were administered at fixed times. The use of extreme dosing intervals of 8-40 h demonstrates that the daily injection time of IDeg can be varied without compromising glycemic control or safety.

One last, but not least important factor in the prevention of hypoglycemic episodes, is a careful analysis of hospital processes and continuous updating and review of the knew how in both medical and nursing staff. The recent study on FADOI-DIAMOND has shown how an educational program involves a continuing improvement in the intra-hospital treatment, resulting in a significant increase in the efficacy and safety of insulin therapy.

Conclusions

Hypoglycemia is a very common problem among hospitalized patients with or without diabetes, associated with higher mortality. Hypoglycemia, related to severe disease and comorbidities, may suggest it as is one marker, rather than a direct cause, of increased risk of mortality. In hospital, mostly in Internal Medicine Wards, it is very important to take all appropriate precautions to avoid hypoglycemic events that might cause adverse outcomes. Fortunately, hypoglycemia is pre-
dictable and preventable if particular attention is given to trigger factors, by overall clinical assessment of patients and the choice of the best treatment options, with implementation of the best specific protocols.

References

34. Fisher BM, Hepburn DA, Smith JG, Frier BM. Respon-


42. Rajendran R, Rayman G. Serious harm from inpatient hypoglycaemia: a survey of hospitals in the UK. Diabetic Medicine 2014 [In press].


