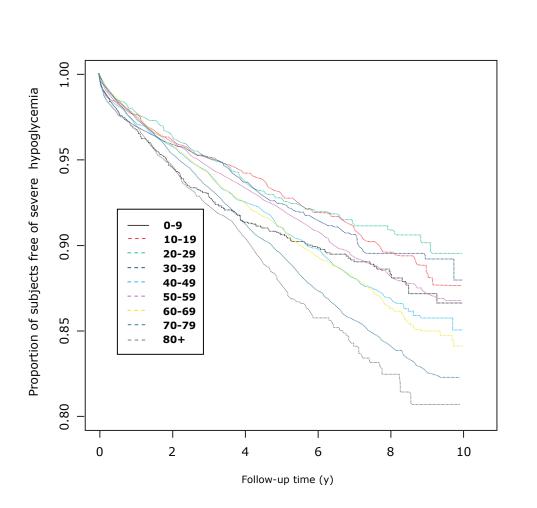
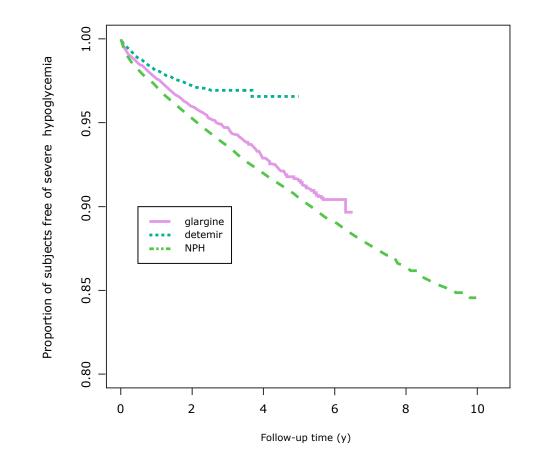
Type of Insulin and Age are Predictors of Hospitalization due to Severe Hypoglycemia: The EpiHypo Study

Incidence and recurrence of severe hypoglycemic (SH) events among patients with diabetes mellitus (DM) was evaluated in a retrospective nation-wide register-based linkage study in Finland. SH was defined as a hospitalization or a secondary health care visit due to DM with severe hypoglycemia (ICD E10.00 or E11.00). Total population (n=140,035) comprised patients who purchased insulin during 2000-2009 and were followed-up for SH events until end of year 2009 or death. The present analysis comprised those 77,046 patients who had not used insulin glargin (IGla), insulin detemir (IDet) or NPH insulin (NPH) before year 2000. Stratified incidence rates with 95% CIs were calculated. Hazard ratios (HR) were estimated by Cox's proportional hazards model. 9,716 SH events were identified. Type of DM (type 1 or 2) was not associated with risk of SH. Compared to IGIa, risk of SH was lower during use of IDet (HR 0.76, CI 0.67-0.87), and higher during use of NPH (HR 1.19, Cl 1.11-1.28) (Fig. 1 upper panel). Female gender predicted lower risk (HR 0.93, CI 0.88-0.98), and increasing age predicted higher risk of SH (Fig.1 lower panel). Risk of SH recurrence was lower during IDet (HR 0.60, CI 0.52-0.69), and higher during NPH (HR 1.58, CI 1.46-1.71) compared to IGla. In conclusion, our data shows that increasing age and type of long-acting insulin are predictors of hospitalization due to SH. Risk of hospitalization due to SH could potentially be modified by selection of long-acting insulin. Figure 1: Occurrence of the first hospitalization or secondary care visit due to SH by type of insulin (upper panel) and by age group (lower panel).





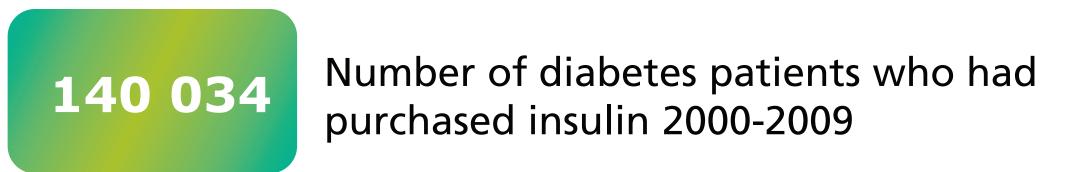
Background

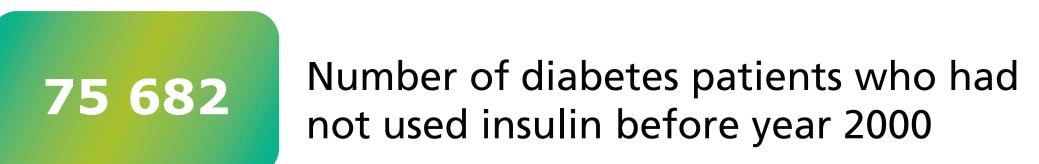
- Severe hypoglycemia (SH) is the most common acute complication of type 1 diabetes.¹
- Increasing use of insulin in type 2 diabetes accompanied with more stringent clinical guidelines for achieving tight glycemic control can potentially increase the incidence of SH.²
- A recent survey in elderly US population showed that insulins were the second most common medication class associated with hospitalization due to adverse drug events, and hypoglycemia accounted for nearly all of these events. 3
- The primary aim of this nationwide retrospective followup study was to evaluate differences in the incidence of hospitalization and secondary health care visits due to diabetes mellitus (DM) with SH between the three long-acting insulins, insulin NPH, insulin glargin and insulin detemir.

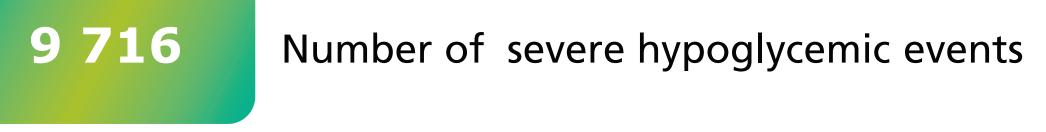
Subjects and methods

- The study cohort contained all patients who were entitled for special reimbursement for diabetes and who had purchased at least one prescription of insulins (ATC code A10A) during the follow-up period 2000-2009.
- The cohort was divided into two populations: insulin naïve patients who initiated the use of IDet, IGla, or NPH during the follow-up time and non-naïve patients with earlier history of insulin use prior to year 2000. The present analysis focuses on the naïve patients.
- Insulin prescriptions were converted into continuous drug exposure periods as 1.15 times the individually scaled number of defined daily doses (DDD) purchased plus a fixed 15 day period to avoid gaps between two consecutive prescriptions.
- SH event was defined as an event which had led to hospitalization or a visit to secondary health care due to severe hypoglycaemia (ICD-10 code E10.00 or E11.00).
- Stratified incidence rates with 95% CIs were calculated.
- Adjusted hazard ratios (HR) with 95% confidence intervals were estimated using the conventional Cox's proportional hazards model with adjustments made for relevant baseline and time-dependent variables: type of diabetes (T1, T2, undefined), age at start of follow-up, gender, concomitant use of other insulins and/or sulfonylureas, switch one insulin to another during follow-up, history of SH events prior to start of follow-up (no, yes), calendar year at the start of follow-up, years from diagnosis of DM at start of follow-up, hospital district.

Figure 1. Description of the patient population







- Among 75682 diabetic patients who had not used long-acting insulin before 2000, 5669 patients experienced a total of 9716 SH events during a mean follow-up time of 4.1 years (Figure 1).
- Type of diabetes (type 1 or 2) was not associated with risk of first SH (Figure 2).
- Concomitant use of other insulins or sulfonylureas increased the risk of first SH (Figure 2). Female gender predicted slightly lower risk of first SH (HR 0.95,
- 95%CI 0.90-1.00) (Figure 2).
- Increasing age predicted higher risk of first SH compared to young adults (Figure 3).
- Incidence of SH was lower during the use of insulin detemir or in sulin glargine in T1 diabetes and during the use of insulin detemir in T2 diabetes (Figure 4).
- In the overall study population, the adjusted risk of first SH compared to NPH was significantly lower during the use of detemir (HR 0.74, 95% CI 0.64–0.85, p<0.001) and glargine (HR 0.88, 95 % CI 0.81-0.97, p=0.006). Risk of first SH during use of detemir was also lower than during use of glargine (HR 0.83, 95% CI 0.73 - 0.95, p=0.006).
- Risk of recurrence of SH was lower during use of detemir compared to NPH (HR 0.54, 95% CI 0.45-0.64, p<0.001) and compared to glargine (HR 0.65,95% CI 0.56-0.75, p<0.001) and during use of glargine compared to NPH (HR 0.83, 95% CI 0.75-0.92, p<0.001).

Figure 2. Hazard ratios for the first severe hypoglycemic event among insulin naïve patients.

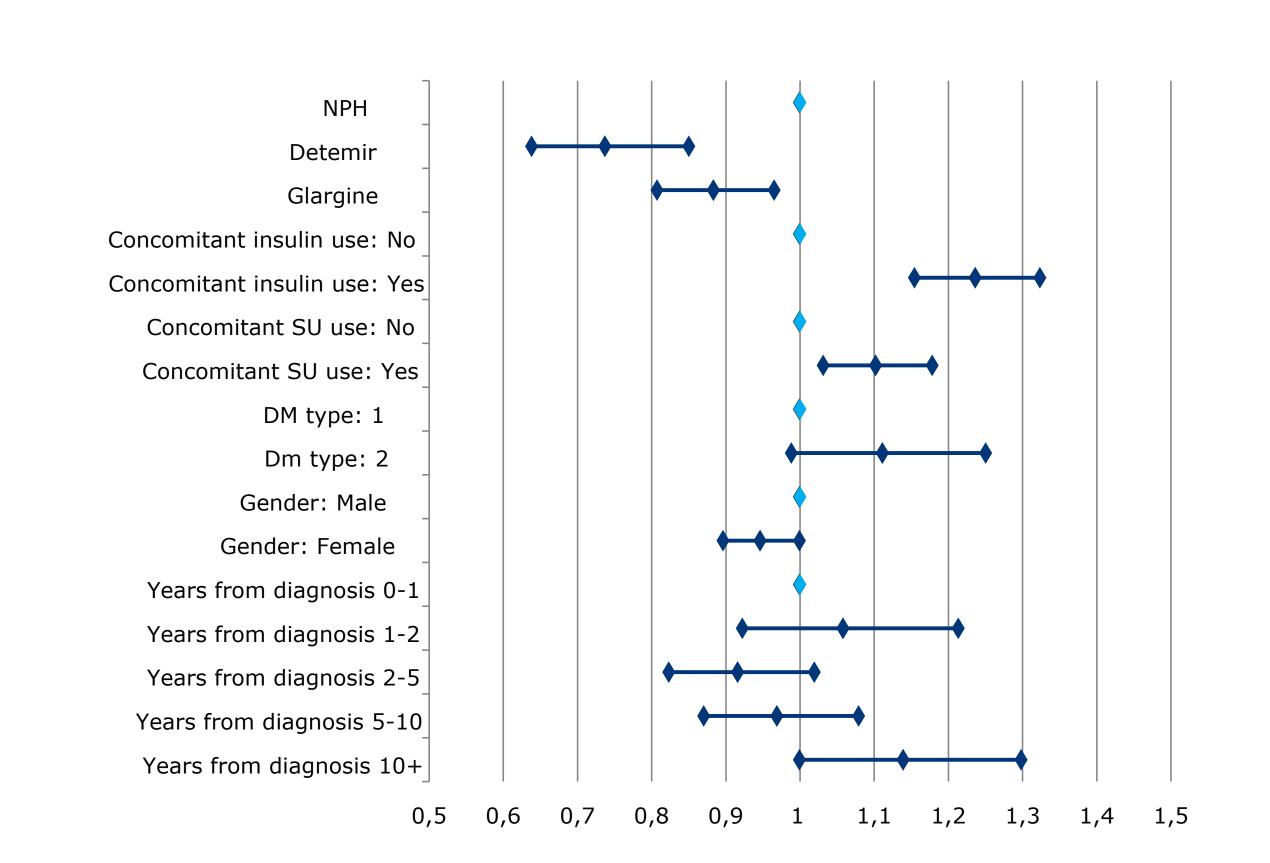
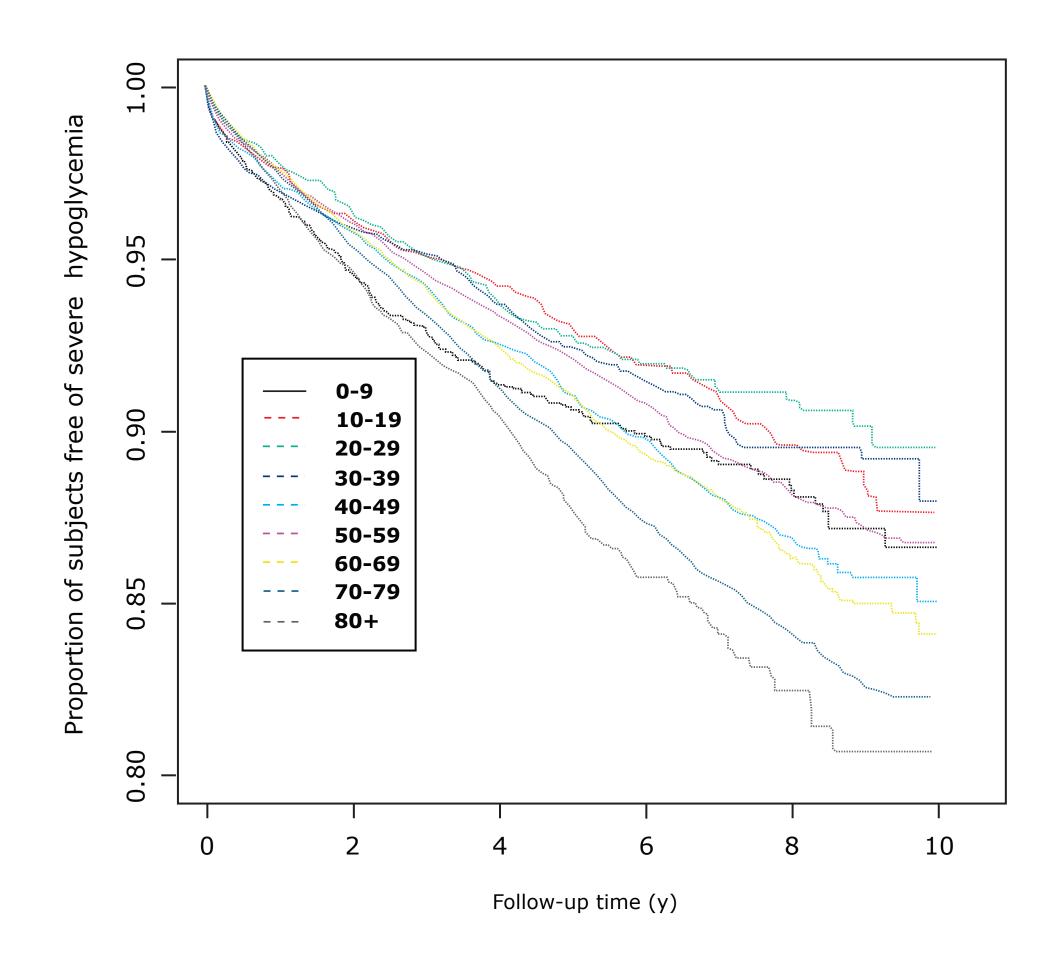


Figure 3. Occurrence of the first hospitalization or secondary care visit due to severe hypoglycemia by age group (left) and by type of insulin (right).



1. Mäkimattila S

2. Korhonen P

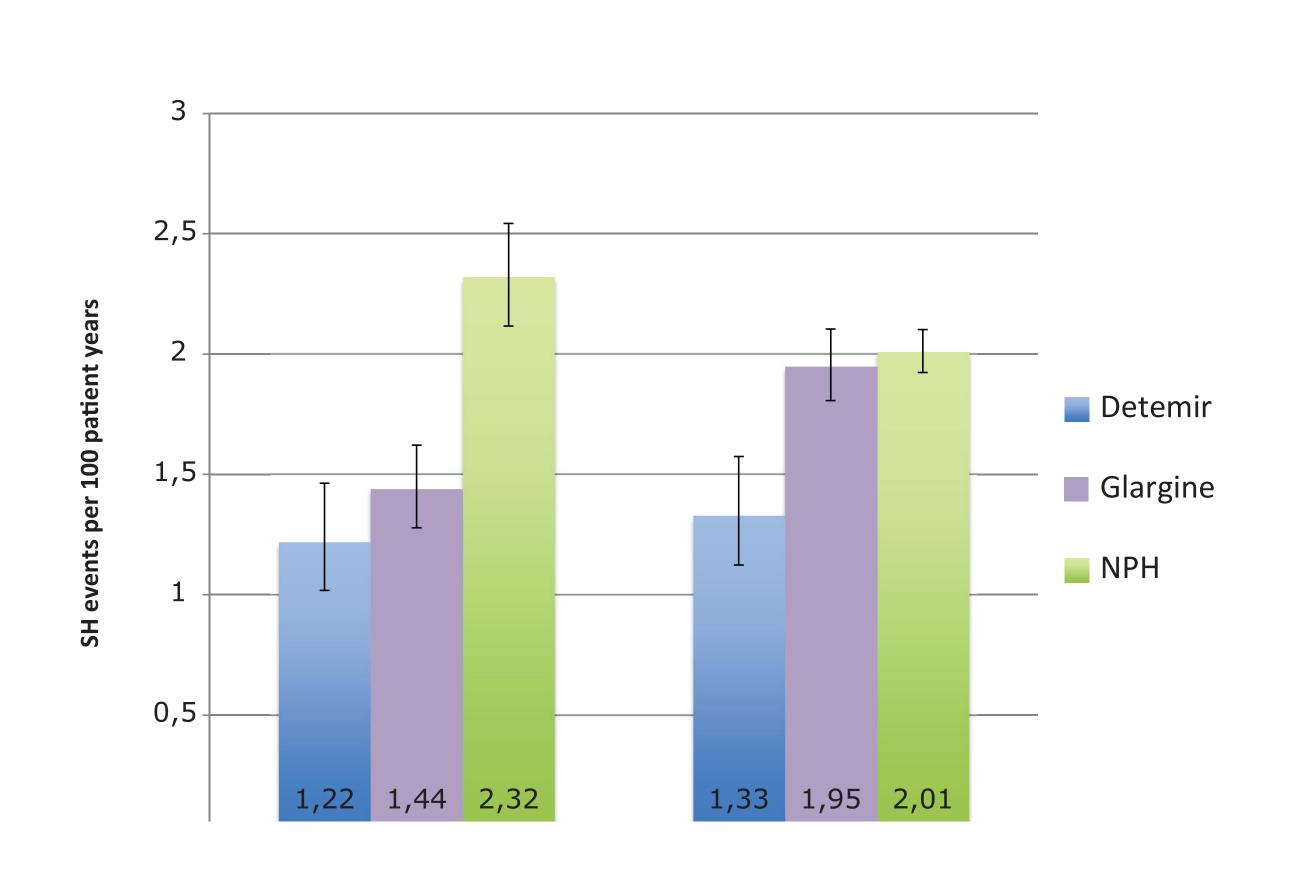
3. Haukka J

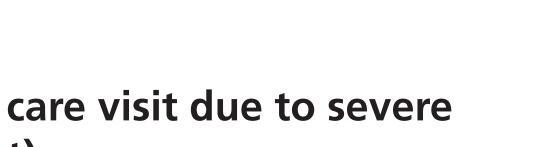
Novo Nordisk Farma, Espoo, Finland

EPID Research Ltd, Espoo, Finland

EPID Research Ltd, Espoo, Finland

Figure 4. Incidence of first severe hypoglycemic event per 100 patient-years among type 1 diabetic and type 2 diabetic patients by type of long-acting insulin used.





4. Hoti F

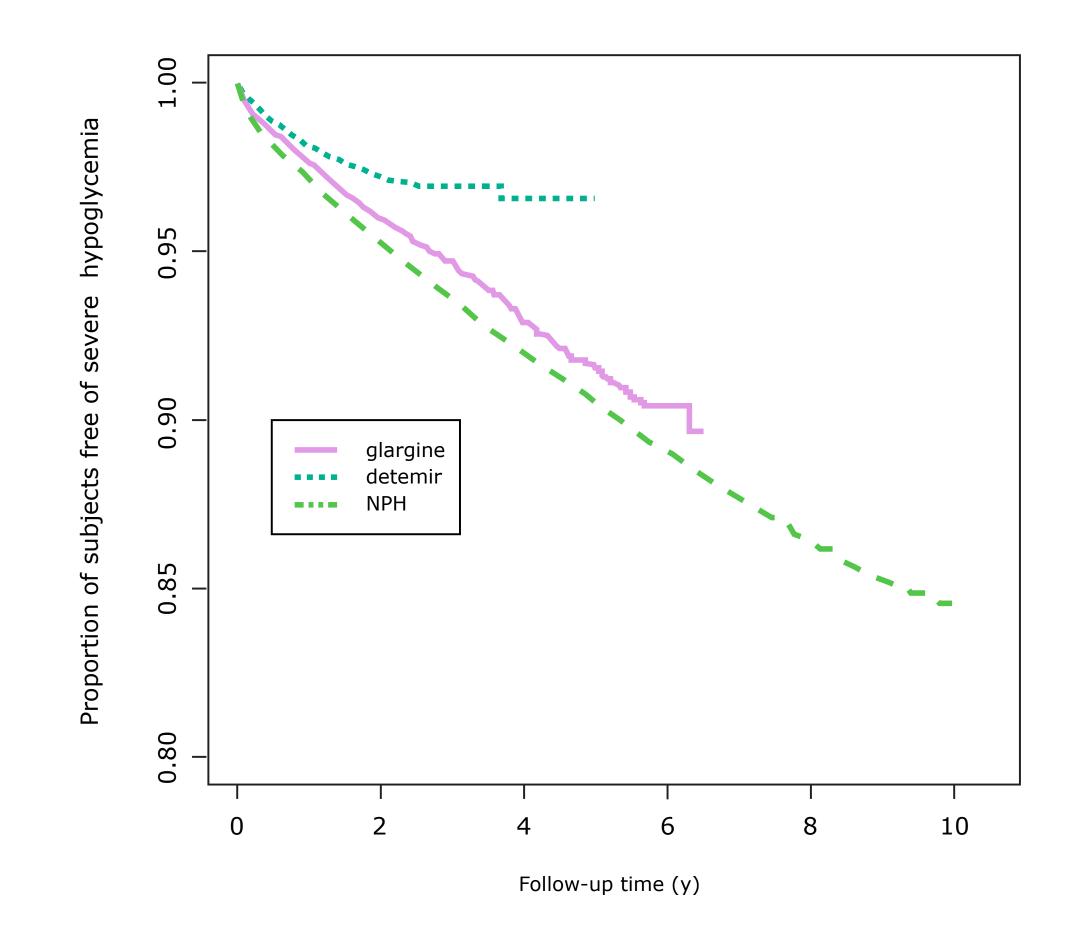
5. Pajunen P

6. Saukkonen T

EPID Research Ltd, Espoo, Finland

Novo Nordisk Farma, Espoo, Finland

Novo Nordisk Farma, Espoo, Finland



References

- 1. The Diabetes Control and Complications Trial Research Group. Diabetes 1997;46:271–86.
- 2. UK Hypoglycaemia Study Group. Diabetologia 2007;50:1140-7.
- 3. Budnitz et al. N Engl J Med 2011;365:2002–12.

Conclusions

- We found significant differences between users of long-acting insulins in incidence of hospitalization or secondary healthcare visit due to SH
- The risk of SH was lowest during use of insulin detemir and highest during use of insulin NPH
- The risk of SH was higher in older age groups and in patients using long-acting insulins together with sulfonylureas or with other types of insulin