Adjusting for the Effect of Switching Basal Insulin Treatment on the Risk of First Severe Hypoglycaemia

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RATIONALE

Long-acting basal insulin analogues have shown a positive effect on the balance between glycaemic control and hypoglycaemia risk compared to NPH (Neutral Protamine Hagedorn) insulin. Hazard ratio (HR) estimates of the risk of severe hypoglycaemia (SH) using standard methods may be biased in the presence of insulin switching.

OBJECTIVES

To estimate and compare the incidence of first SH among type 2 diabetes mellitus (T2DM) patients treated with insulin detemir, glargine or NPH, accounting for insulin switching with the use of Marginal Structural Models (MSM).

METHODS

T2DM patients aged > 40 who initiated use of detemir, glargine or NPH were identified from the Finnish health care registers. The patients were followed until discontinuation of insulin treatment, death, end of 2009 or first SH event. In the MSM the causal effect of insulin use on the risk of first SH was estimated by applying the inverse of the probability to switch as weights in the Cox's Proportional Hazards (Cox PH) model. The probability to switch (from NPH to detemir or glargine) was estimated using logistic regression adjusting for both time fixed and time dependant covariates on several time grids.

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The Ethical Committee approval

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Research permissions

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- Statistics Finland (TK-53-367-11)

ENCePP reference

- EUPAS2278

DATA SOURCES

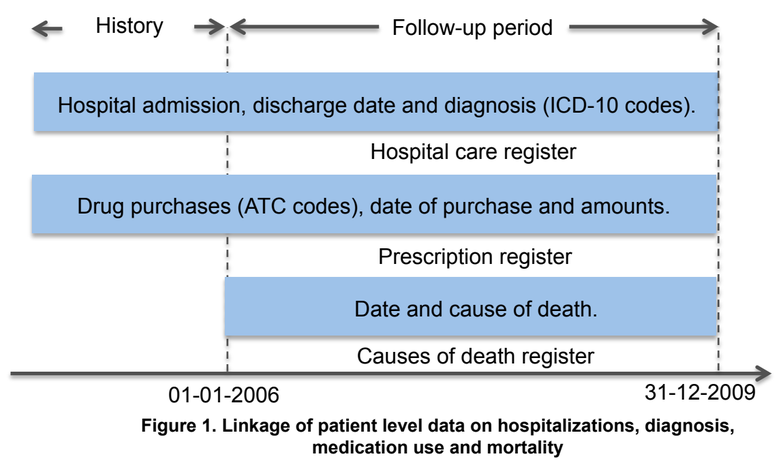

Figure 1. Linkage of patient level data on hospitalizations, diagnosis, medication use and mortality

Total number of patients	27 267
Total person-years	24 301
Mean follow-up time (years)	0.9
Total Number of SH events	250

SWITCH SUMMARY

Switch from NPH to detemir	
Number of patients, N (%)	593 (5.93 %)
Days to first switch, Mean (± SD)	434.57 (305.48)
Switch from NPH to glargine	
Number of patients, N (%)	936 (9.37 %)
Days to first switch, Mean (± SD)	358.75 (280.90)
Switch from detemir to NPH	
Number of patients, N (%)	24 (0.45 %)
Days to first switch, Mean (± SD)	122.17 (126.02)
Switch from detemir to glargine	
Number of patients, N (%)	148 (2.80 %)
Days to first switch, Mean (± SD)	168.35 (198.57)
Switch from glargine to NPH	
Number of patients, N (%)	56 (0.47 %)
Days to first switch, Mean (± SD)	159.23 (214.66)
Switch from glargine to detemir	
Number of patients, N (%)	168 (1.40 %)
Days to first switch, Mean (± SD)	293.12 (229.62)

STUDY POPULATION

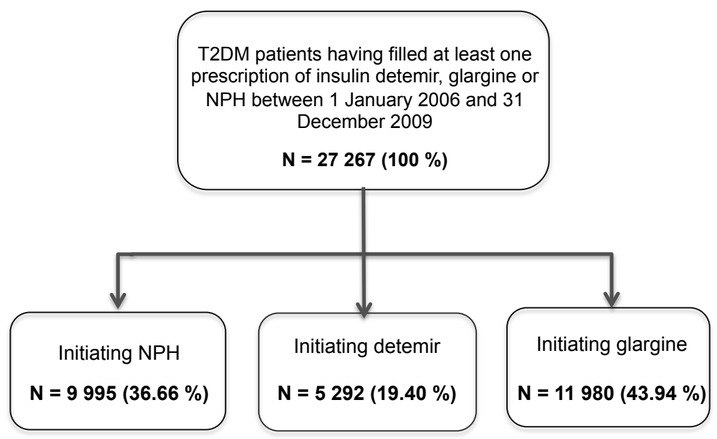

Figure 2. Description of the study population

Age (years)			
Mean (± SD)	66.87 (± 12.17)	64.75 (± 11.82)	66.59 (± 12.31)
Gender			
Male, N (%)	5731 (57.34 %)	3065 (57.92 %)	6967 (58.16 %)
Years from diagnosis			
Mean (± SD)	6.33 (± 6.03)	6.42 (± 6.10)	6.85 (± 6.38)

INVERSE PROBABILITY WEIGHTS

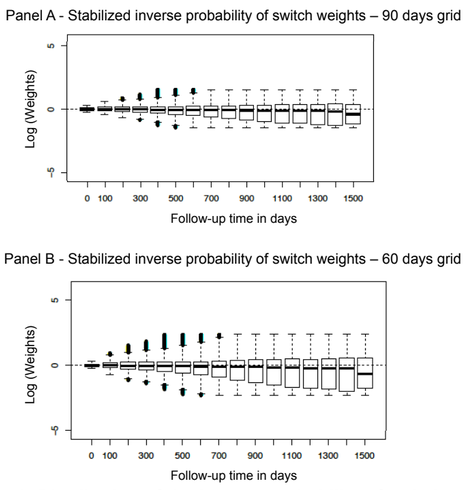

Figure 3. Distribution of the inverse probability of switch weights, 90 days and 60 days grids

Distribution of the inverse probability of switch weights estimated using the 90 days (Figure 3. Panel A) and the 60 days (Figure 3. Panel B) grids. The probability of insulin switch was estimated adjusting for the following covariates:

- Age at start of follow-up.
- Gender.
- Use of sulfonylurea (Time-dependent).
- Use of other insulin (Time-dependent).

RESULTS

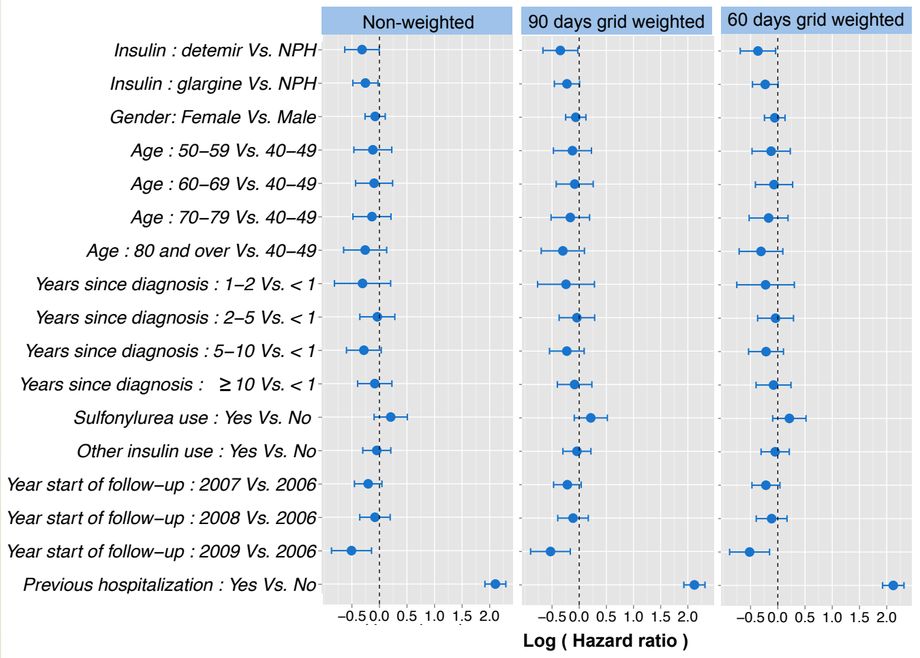

Figure 4. Hazard ratio estimates of the risk of severe hypoglycaemia
Left panel: traditional Cox PH model.
Middle panel: MSM with a 90 days grid weights.
Right panel: MSM with 60 days grid weights.

During a mean follow-up of 0.9 years, 250 (0.92 %) patients were hospitalized for severe hypoglycaemia.

HR estimates using the traditional cox PH model adjusting for age, gender, years since diagnosis, sulfonylurea use, other insulin use, year of start of follow-up and previous hospitalization showed that the use of insulin detemir and glargine was associated with lower risk of SH when compared to NPH, The hazard ratios being 0.73 (95% CI 0.53 – 1.00) and 0.78 (95% CI 0.62 – 0.97) respectively

Estimates from the MSM used to adjust for the effect of insulin switch as well as other covariates were derived by applying the inverse of the probability of switch as weights in the Cox PH model. The weights were calculated using a 60 days and a 90 days time grid, the mean weights were 1.04(± 0.30) and 1.06 (± 0.39), respectively.

In the MSM, using a 60 days time grid, the HR first SH for insulin detemir and glargine compared to NPH was 0.71 (95% CI 0.51 – 0.98) and 0.80 (95% CI 0.63 – 1.01)

In the MSM, using a 90 days time grid, the HR first SH for insulin detemir and glargine compared to NPH was 0.70 (95% CI 0.50 – 0.96) and 0.79 (95% CI 0.63 – 1.01)

Results were similar for 30 and 180 days time grids.

CONCLUSIONS

- The benefit of using detemir or glargine over NPH remains after accounting for measured confounding on insulin switch by MSMs.
- The results were very similar for different time grids (30 -180 days). The natural scale of prescription changes is 90 days.
- Further studies with more variables predicting switches are needed to account for unmeasured confounding on insulin switch.

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Strandberg AY, Hoti FJ, Strandberg TE, Christopher S, Haukka J, Korhonen P. All-cause and cause-specific mortality among users of basal insulins NPH, detemir and glargine. PLoS One 11(3), 2016.

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