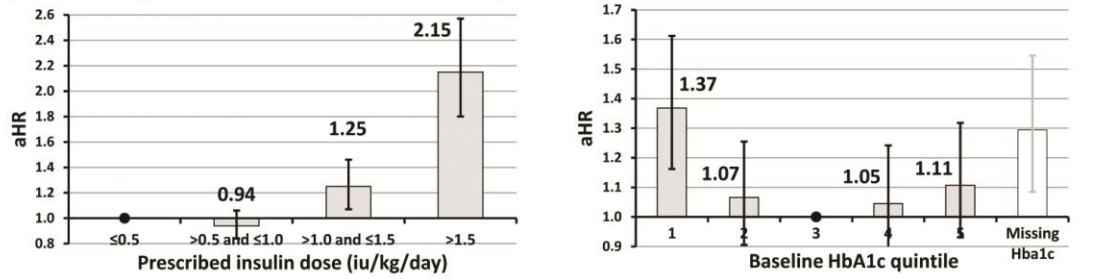
Exogenous insulin and risk of all-cause mortality in type 2 diabetes: a dose-response association

S.E. Holden[1], G. Schernthaner[2], S. Jenkins-Jones[3], C.J. Currie[1];
[1]School of Medicine, Cardiff University, UK, [2]Department of Medicine, Rudolfstiftung Hospital Vienna, Austria, [3]Pharmatelligence, Cardiff, UK.

Background and aims: Along with a clinical and biological rationale, epidemiological data have emerged that raise questions about the widespread use of exogenous insulin in people with type 2 diabetes. In the absence of specifically designed randomised trials, here we explore the hypothesis that if insulin increases the risk of death in these people, there should be a dose-response association.
Materials and methods: Data were from a 10% sample of the UK population available from the Clinical Practice Research Datalink. Using strict data quality criteria, subjects with type 2 diabetes were selected if they had progressed to treatment with insulin. The first prescription of insulin was used as the index date. Annual, average, weight-based, prescribed insulin dose was estimated by attributing a quantity to recorded prescriptions. Our outcome was all-cause mortality, and the risk of death was evaluated in Cox models that accounted for common risk factors. Dose was evaluated as a time-dependent covariate. Prescribed dose categories were set at ≤0.5, >0.5 and ≤1.0, >1.0 and ≤1.5, and >1.5 iu/kg/day using the lowest dose as the referent.
Results: We identified 8,414 people exposed to an insulin-only regimen and receiving at least two consecutive prescriptions for insulin. Of these, 7,538 patients had complete insulin dose (with an average dose ≤4iu/kg/day), weight and time-to-event information; 2,193, 3,818, 1,013 and 514 patients were allocated to the ≤0.5, >0.5 and ≤1.0, >1.0 and ≤1.5, and >1.5 iu/kg/day insulin-dose groups, respectively, in year 1. The overall mean age at baseline was 64.6, 64.7, 64.4 and 64.9 years; 63%, 55%, 51% and 47% were males; and average HbA1c at baseline was 9.2%, 9.7%, 9.9% and 9.6% for each increasing dose category, respectively. The risk of death increased in the lowest HbA1c quintile and above 1.0 iu/kg/day (figure) in a generally increasing pattern. The pattern of association with dose was consistent in a number of phenotypic sub-groups such as those with good glucose control at baseline. In comparison with the low-dose insulin group (≤0.5iu/kg/day), adjusted hazard ratios for the high-dose group (>1.5iu/kg/day) were 1.36 (0.56-3.34), 1.43 (0.87-2.35), 2.04 (1.52-2.75) and 2.89 (2.22-3.77) for patients aged ≤55, >55 and ≤65, >65 and ≤75, and >75 at baseline.
Conclusion: There was a dose-response association between insulin and the risk of death in subjects with type 2 diabetes. Those progressing to insulin therapy in older age and with good glucose control were at particularly high risk.

Figure

Adjusted hazard ratios (aHRs) for all-cause mortality by insulin dose group and by baseline HbA1c quintile using Cox proportional hazards model, with insulin dose added as a time dependent covariate



Adjusted hazard ratios for the high dose insulin group (>1.5 iu/kg/day) compared to the low dose insulin group (<0.5) when the analysis is split by age group and by morbidity (Charlson Index)