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Use of Analog and Human Insulin in a European Hemodialysis Cohort With Type 2 Diabetes: Associations With Mortality, Hospitalization, MACE, and Hypoglycemia

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Abstract

Rationale & Objective: Poor glycemic control may contribute to the high mortality rate in patients with type 2 diabetes receiving hemodialysis. Insulin type may influence glycemic control and its choice may be an opportunity to improve outcomes. This study assessed if treatment with analog insulin compared to human insulin is associated with different outcomes in people with type 2 diabetes and kidney failure receiving hemodialysis.

Study Design: Retrospective cohort study.

Setting & Participants: People in the Analyzing Data, Recognizing Excellence and Optimizing Outcomes (ARO) ii study with kidney failure commencing hemodialysis and type 2 diabetes being treated with insulin within 288 dialysis facilities between 2007 and 2009 across seven European countries. Study participants were followed for 3 years. People with Type 1 diabetes were excluded using an established administrative data algorithm.

Exposure: Treatment with an insulin analog or human insulin.

Outcomes: All-cause mortality, major adverse cardiovascular events, all-cause hospitalization, and confirmed hypoglycemia (blood glucose <3.0 mmol/l sampled during hemodialysis).

Analytical Approach: Inverse probability weighted Cox-proportional hazards models to estimate hazard ratios for analog insulin compared to human insulin.

Results: There were 713 insulin analog and 733 human insulin users. Significant variation in insulin type by country was observed. Comparing analog to human insulin at three years, the percentage of patients experiencing endpoints (and adjusted hazard ratios) were 22.0% vs 31.4% (0.808, 95%CI 0.66 to 0.99, p=0.04) for all-cause mortality, 26.8% vs 35.9% (0.817, 95% CI 0.68 to 0.98, p=0.03) for MACE, and 58.2% vs 75.0% (0.757, 95% CI 0.67 to 0.86, p<0.001) for hospitalization. Hypoglycemia was comparable between insulin types at 14.1% vs 15.0% (1.169,

95% CI 0.80 to 1.72, p=0.4). Consistent strength and direction of the associations were observed across sensitivity analyses.

Limitations: Residual confounding, lack of more detailed glycemia data.

Conclusions: In this large multinational cohort of people with type 2 diabetes and kidney failure receiving maintenance hemodialysis, compared to human insulin, treatment with analog insulins was associated with better clinical outcomes.

Index Words: Hemodialysis, mortality, major adverse cardiovascular events, Type 2 diabetes, insulin

Plain Language Summary

People with diabetes who are receiving dialysis for kidney failure are at high risk of cardiovascular disease and death. This study uses information from 1446 people from seven European countries who have kidney failure, are receiving dialysis, have type 2 diabetes, and are prescribed either insulin identical to that made in the body (human insulin) or insulins with engineered extra features (insulin analog). After three years, fewer participants receiving analog insulins had died, had been admitted to the hospital, or had a cardiovascular event (heart attack, stroke, heart failure or peripheral vascular disease). These findings suggest that analog insulins should be further explored as treatment leading to better outcomes for people with diabetes on dialysis.

Introduction

Diabetes is a major risk factor for developing chronic kidney disease (CKD) and the leading cause of kidney failure (KF) in the Western world.[1] According to the International Diabetes Federation (IDF) atlas,[2] the number of patients with diabetes will continue to rise from currently about 537 million to 643 million in 2030. Importantly, non-diabetic patients with KF have a very high mortality[3] due to different pathomechanisms.[4,5] Diabetes further increases the risk for all-cause and cardiovascular mortality,[6] and patients with type 2 diabetes[7] on hemodialysis (HD) have a very poor prognosis.

Importantly, patients with diabetes and KF show much higher rates of hypo- and hyperglycemic crises compared to non-KF high-risk populations with diabetes. Poor glycemic control in KF patients on HD[8] or prior to dialysis initiation[9] has been associated with higher mortality risk. As CKD progresses insulin clearance decreases[10] leading to increased glycemic variability in patients with KF treated with exogenous insulin[11], driving insulin dosage adjustments. Exogenous human insulin (i.e. rapid- and long-acting) has several clinical shortcomings, including postprandial hyperglycemia followed by hypoglycemia and weight gain.[12] Consequently, rapid- and long-acting insulin analogues have been designed to better imitate the endogenous insulin response in healthy individuals.[12] Novel insulin analogues translate into better glycemic control[13] and lower glycemic variability[14] in the general population with diabetes. However, in clinical trials in these patients, no differences in mortality and major adverse cardiac events (MACE) have been found when comparing analogue and human insulins.[15-17]

Given that HD significantly contributes to an increased glycemic variability,[18] the vulnerable nature of patients with type 2 diabetes on HD treatment,[19] and the fact that CKD/KF represents a

major global disease burden in patients with diabetes,[20] there is a need for therapeutic improvements in the management of patients with type 2 diabetes receiving HD. To determine if analogue insulin compared to human insulin is associated with different outcomes in this group, we performed analyses of a large multicenter cohort of incident HD patient[21] with type 2 diabetes from >250 Fresenius Medical Care (FMC) dialysis centers out of seven participating countries using causal inference techniques.

Methods

Cohort & Data

The Analyzing Data, Recognizing Excellence and Optimizing Outcomes (ARO) ii cohort was a prospective observational cohort study of incident HD patients enrolled at one of the 312 Fresenius Medical Care (FMC) facilities across 15 European countries between 2007 and 2009. Although the original cohort study had follow-up until 2014, patients under follow-up at this timepoint were small. For the current analysis follow-up ends in 2012. ARO used electronic medical records to capture anonymized longitudinal individual-level data.[22] All local ethical and regulatory obligations concerning patient data for each of the 15 participating countries were met at the time of data collection, and the institutional review board from the Medical University of Innsbruck [EK-Nr. 1339/2020] has approved the current analysis. Informed consent was obtained from all patients by FMC Europe. For purposes of this study, analysis was limited to countries providing at least 10 HD patients with type 2 diabetes on insulin treatment.

Data on demography, comorbidity, laboratory, hospitalization, mortality, medications and individual HD sessions were available. The presence of six comorbid conditions were recorded using International Classification of Diseases (ICD) 10 codes from administrative data using existing schema (ischemic heart disease, congestive heart failure, cerebrovascular accident,

peripheral artery disease, chronic obstructive pulmonary disease, dysrhythmia).

Eligibility, Insulin Exposure and Follow-up

Participants in AROii were assessed for eligibility throughout their follow-up. They were considered eligible if they were identified as having type 2 diabetes, receiving either a human or analogue insulin, with analysis starting at the date of first prescription of these insulins while receiving dialysis, with the date of first dialysis being the start of follow-up for patients who were on insulin before starting HD. If a patient developed diabetes having already begun HD, follow-up would begin when insulin was first prescribed. Patients who were switched between analogue and human insulins during the follow up were excluded. Because ICD10 coding defines individuals with diabetes as "Insulin Dependent" or "Non-Insulin Dependent" rather than type 1 and type 2, an existing validated administrative data algorithm was applied to HD patients with the codes of E10 or E11 to differentiate between type 1 and type 2 diabetes using the combination of age at onset of diabetes, current age, previous diabetic ketoacidosis and insulin pump use as described recently.[23] Analogue or human insulin therapy, as well as concomitant oral antidiabetic medication (Table S1), were identified using the Anatomical Therapeutic Chemical (ATC) Classification System medication codes with review of the free text supplied with the medications to confirm correct assignment to the respective ATC groups and associated human or analogue insulin type (Table S2). Follow-up was three years, censored for transfer out of an FMC facility, transplantation, recovery of kidney function or change in dialysis modality.

Endpoints

All-cause mortality was defined as death while receiving HD for kidney failure. Hospitalization, MACE and hypoglycemia were analyzed as time from first insulin prescription while receiving HD to first corresponding event. These endpoints have the competing events of

death while receiving HD, or the censoring events above. A hospitalization event was defined as an admission to hospital lasting at least one day. A MACE event was defined as hospitalization with the primary reason for admission corresponding to the ICD10 codes of coronary, cerebral, or peripheral arterial events, heart failure or cardiac arrest (Table S3). According to the joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes,[24] a hypoglycemia event was defined as a laboratory glucose of <3.0 mmol/l (i.e. level 2 hypoglycemia). Glucose measurements were commonly performed with bloods performed to monitor HD and KF as part of routine clinical care at the beginning of HD, although glucose measurements performed at other times were available. We report the frequency of glucose monitoring using this method for each arm and by country (Table S4). The study did not have access to capillary glucose monitoring routinely used by patients to monitor glycemic control and did not capture if the participant had symptoms associated with any glucose measurement.

Statistical Methods

Numbers of missing data for each variable are shown in Table S5. To visualize the event rates stratified by insulin type, accounting for the competing risk of death we report cumulative incidence function graphs.[25] Proportional hazards models are reported using inverse probability weighting (IPW), and multiple imputation in accordance with best practices was performed.[26] First, multiple imputation of the variables included in the weighting and endpoint models, predicted using these variables and the endpoints, was undertaken using predictive mean matching-generated twenty datasets. This imputation method is more robust to assumptions around linearity.[27] Second, for each imputed dataset logistic regression was used to obtain probabilities of analogue insulin prescription using baseline covariates (age (<=50,>50-60,>60-

70,>70-80,>80), sex, six comorbid conditions [Table S5], albumin (<=35,>35 g/L), phosphate (<=0.8, >0.8-1.5, >1.5 mmol/L, calcium (<=2.1, >2.1-2.6, >2.6 mmol/L), hemoglobin (<100,100-120,>120 g/L), glycated hemoglobin (HbA1c, <=6%, >6-7,>7-8,>8-9,>9), erythropoiesis stimulating agents (because of their impact on red-cell turnover and therefore HbA1c, <2000, 2000 to <6000, 6000-<12000, >=12000 units per week), time on dialysis (<1 or >=1 year), and body mass index (BMI, <21, 2 unit increases then >35 kg/m^2)). Probabilities from these logistic regression models are converted into weights from the reciprocal of the probabilities estimated from the baseline covariates to generate a well-balanced pseudopopulation (table S6). Stabilization of weights was not required (mean unstabilized weight 1.001, SD 0.431 using all twenty datasets). Comparing analogue to human insulin, we report the rate in person-years and the absolute proportion of patients experiencing the endpoints of all-cause mortality, MACE, all-cause hospitalization, and hypoglycemia (< 3mmol/l) at three years using the weighted dataset, and finally perform adjusted Cox-proportional regressions reporting pooled estimates across the twenty imputed datasets. The inclusion of imputed adjustment variables in our second stage ensures that uncertainty around the imputed adjustment variables is accommodated in endpoint estimates and has the capacity to further reduce bias. In Table S7, we present relevant data from the multiple imputation process according to the standardized reporting guidelines adapted from Sterne et al.[28]

We also conducted a number of subgroup analyses. Hazard ratios for cardiovascular and non-cardiovascular mortality analyses are reported separately. We further estimated endpoints stratified by age, sex, BMI (<30 vs. ≥30 kg/m²), geography (Central/Eastern Europe: Czech Republic, Hungary, Turkey; Western Europe: United Kingdom, Italy, Portugal, Spain), re-estimating the weights for these sub-populations (re-estimated weights reported in Table S8). To

explore if glucose variability differed between insulin types, we estimated the coefficient of variation for glucose measurements for each individual patient and estimated a mean coefficient of variation by insulin type. This analysis excluded patients from the United Kingdom and Portugal who had lower sampling rates than other participating countries. To explore if differences in outcomes could be explained by glycemic control, we present lowess smoothing plots of HbA1c for the duration of the analysis, stratified by insulin type. All analyses were undertaken in R version 4.1, with the packages "mice" and "ipw" to perform multiple imputation and IPW, respectively.

Results

Cohort and demography

Among 10,637 patients commencing HD across 15 countries, 3,783 were identified as diabetic subjects based on ICD10 codes of whom 1,899 were prescribed insulin prior to or while receiving HD. Of these, 239 were identified as type 1 diabetes using the administrative algorithm (Figure S1), and were therefore excluded from the analysis. A further 52 subjects were removed as they were from countries providing fewer than 10 patients, along with 162 patients who received a mixture of human and analogue insulins, leaving 1,446 patients recruited from 288 facilities across seven countries for the present analysis, with a total of 2855 patient-years follow-up (1.97 years per patient). Insulin was commenced prior to or within 90 days of starting HD in 69.8% (1,009 patients). The study flow diagram is shown in Figure S2. There was only a small proportion of patients (N=75) receiving oral antidiabetic medication at 90 days from starting HD.

The demography, comorbidities, and laboratory variables stratified by insulin type are shown in Table 1 and demonstrate older patients with more baseline comorbidities in the human insulin

group, but worse glycemic control in the analogue group. Although use of the two insulins was approximately evenly split across the entire cohort, there was significant variation across the seven countries (Table S9): the proportion of patients in each insulin group by country is shown by increasing gross domestic product per capita in Figure 1, suggesting no clear relationship.

Association between analogue vs human insulin and endpoints

Within the 1,446 patients included in the adjusted analysis, there were 387 deaths (173 cardiovascular, 186 non-cardiovascular, and 28 unknown), 965 first hospitalizations, 454 first MACE events, and 138 first hypoglycemic events (< 3mmol/l sampled on HD) over a median follow-up of 27.7 months. Cumulative Incidence Function plots stratified by analogue and human insulin are presented in Figure 2 with proportions experiencing events in Table 2. Analogue insulin was associated with superior event-free survival for the primary endpoints of all-cause mortality, MACE, and hospitalization. Hypoglycemia, restricted to countries in which it was assessed regularly at dialysis (United Kingdom and Turkey removed, remaining n=958), was comparable with both insulins.

Multi-variable adjustment for demography, biochemical parameters, and comorbidities using doubly adjusted IPW estimated the hazard ratios [95% confidence interval (CI)] for all-cause mortality of 0.808 [0.659-0.991] (p=0.04); MACE 0.817 [0.680-0.983] (p=0.03); hospitalization 0.757 [0.665-0.861] (p<0.001) and hypoglycemia 1.169 [0.796 – 1.718] (p=0.4) (Table 2). Cardiovascular and non-cardiovascular specific-mortality hazard ratios for analogue versus human insulin were 0.734 [0.541-0.996] (p=0.05) and 0.834 [0.617-1.128] (p=0.2) in the adjusted IPW analysis (Table 2). When the components of the MACE endpoint were analyzed separately (Table 2), results remained similar in terms of effect strength and direction. The mean coefficient of variation of glucose levels measured on HD, in countries performing it regularly,

was 0.328 for the analogue insulin group and 0.326 for the human insulin group (t-test p=0.9), and the trajectory of HbA1c in the two groups were not visually different (Figure 3).

Subgroup Analyses

Subgroup analyses showed consistent direction of effect in favor of analogue insulin for different subgroups of age, BMI, sex, and geographical region (Figure 4), with significant interaction between insulin type and geographical region for MACE and hospitalization (Table S8). Ethnicity was not captured by this study.

Discussion

Using a large, pan-European, multicenter cohort of incident HD patients with type 2 diabetes, we show that analogue insulin therapy is associated with lower all-cause mortality, MACE, and hospitalization compared to human insulin therapy, while level 2 hypoglycemia (<3.0 mmol/l) on HD and glycemic variability remained similar compared to human insulin.

Patients with KF treated by HD have a shortened lifespan with a difference of >25 years when compared to the general population.[1] In individuals with type 2 diabetes, KF is associated with an excess mortality rate compared to non-KF individuals with type 2 diabetes.[29] Importantly, patients with type 2 diabetes on HD are excluded from most of the cardio-renal-protective glucose-lowering medications, including sodium–glucose cotransporter 2 (SGLT2) inhibitors,[30] and insulin therapy is the cornerstone of antihyperglycemic treatment in KF.

In contrast to our findings in people with type 2 diabetes and KF on hemodialysis, in the general diabetic population, analogue compared to human insulin treatment is not associated with differences in mortality and MACE outcomes.[15-17] Neugebauer et al.[15] demonstrated similar rates of all-cause and cardiovascular mortality, as well as MACE, using a retrospective dataset from four US health care delivery systems comprising 127,600 adults with type 2 diabetes,

however the adjustment for time-varying HbA1c means that any advantage mediated through improved glycemic control would be neutralized. Fullerton et al.[16] summarized data from randomized controlled trials on short-acting insulins and found no clear difference between analogue and human insulin, similar to a recent Cochrane review.[16] There is no trial which has been designed to investigate long term effects, i.e. on mortality and MACE, in participants with diabetes-related microvascular complications, such as CKD. We believe that in general type 2 diabetes cohorts (not including people with CKD/KF) other factors and co-variates may counterbalance any potential differences between analogue vs. human insulin, for instance concomitant use of other (cardio-renal) protective glucose-lowering and/or lipid-lowering treatment. Notably, as statins do not decrease mortality and MACE in type 2 diabetes patients receiving HD,[8] lipid-lowering treatment is unlikely to contribute to the observed effects.

Pathophysiologically, different mechanisms for both long- and short-acting analogues could potentially explain the improved outcome of patients on analogue insulins in our cohort. A recent meta-analysis in individuals with type 1 diabetes showed that analogue insulin therapy was associated with lower total, nocturnal, and severe hypoglycemia risk, as well as reduced postprandial glucose and HbA1c.[31] In type 2 diabetes long-acting analogues do not result in insulin peaks compared to long-acting human insulins, i.e. neutral protamine Hagedorn insulin, thereby reducing hypoglycemia risk.[32] In contrast, short-acting analogues induce a faster and higher peak plasma insulin concentration in the first hour after injection compared to human short-acting insulin, thereby reducing the adverse postprandial glucose peak.[33] Both, long- and short-acting, analogues, therefore, could significantly reduce glycemic variability, which has been linked to mortality in people on HD,[34] without necessarily modifying HbA1c. Two recent retrospective population-based cohort studies from UK and Taiwan have also reported beneficial

effects of (long-acting) analogue insulin with respect to cardiovascular outcomes, as well as hypoglycemic risk, supporting our findings in this more vulnerable cohort.[35,36]

Cumulative incidence curves for mortality, MACE, and hospitalization outcome separated as early as the first months of follow-up, i.e. around initiation of HD. This is in accordance with observational data from the same cohort,[37] demonstrating an increased risk of hospitalization, MACE, and mortality in patients soon after the start of HD. Hypothetically, after patients have experienced an early outcome and dropped out, longitudinal trends stabilize over the study period and run in parallel (Figure 2) in our cohort. In addition, some patients already started analogue insulins before being included in our study and potential beneficial treatment effects of analogue insulins could have accumulated prior to starting HD.

Some limitations of the present study need to be highlighted. Although we have performed multivariable analyses adjusting for many clinically relevant covariates, residual confounding cannot be excluded. In particular we had restricted access to information on socioeconomic status of the participants, as increased costs of analogue insulin in some geographies may introduce bias. Even though the number of missing data for some variables was low, it required the use of multiple imputation. We did not have access to the more sensitive self-monitored blood glucose measurements to thoroughly assess glycemic variability. Because of the time-varying nature of insulin prescriptions it was not feasible to investigate different insulin regimens (e.g. basal insulin-only vs. basal-bolus insulin regimen) or different types of analogues (e.g. fast- vs. long-acting) separately. We acknowledge that excluding the small number of patients who switched between insulin types could introduce bias and does not utilize all available data. The study's strengths include the potentially high relevance for daily practice as there is an unmet need to improve the prognosis of individuals with type 2 diabetes and KF. Furthermore, we have

applied sophisticated statistical analyses with robust adjustment for multiple variables using a validated clinical database, and analyzed many patients using well-defined outcomes. Prospective, adequately designed and powered clinical trials should investigate whether switching from human insulin to analogue insulin improves patient-relevant outcomes in people with KF and the cost-effectiveness of this intervention.

In conclusion, in a large, multinational cohort of HD patients with type 2 diabetes, analogue compared to human insulins were associated with better clinical outcomes, although hypoglycemia rates were increased. Analogue insulins may represent a superior therapeutic option for this group of patients with high unmet needs.

Supplementary Material

Supplementary File (PDF)

Figure S1: Decision tree for the identification of patients with type 1 diabetes (T1D) or type 2 diabetes (T2D) with patient numbers

Figure S2: Study flow diagram

Table S1: Overview on the Anatomical Therapeutic Chemical (ATC) classification system medication codes used to identify non-insulin glucose-lowering therapies

Table S2: Overview on the Anatomical Therapeutic Chemical (ATC) classification system medication codes used to identify analogue or human insulins, as well as pre-mixed insulins

Table S3: Overview on the International Classification of Diseases (ICD) 10 codes used to identify comorbidities and complications

Table S4: Frequency of glucose monitoring according to country of the dialysis facility and insulin type, as well as insulin type stratified by each country

Table S5: Number of missing data for each variable stratified by the two study groups (i.e., human insulin vs. analogue insulin treatment)

Table S6: Baseline characteristics stratified by the two study groups (i.e. human insulin vs. analogue insulin treatment) in the observed population (presented in Table 1), as well as the inverse probability weighted pseudo-population

Table S7: Multiple Imputation Reporting

Table S8: Summary statistics for inverse probability weights for subgroup analyses and interaction term p-values

Table S9: Demographics of analogue and human insulin users by country

Article Information

Additional Information: Dr Fotherinham's ORCiD is 0000-0002-8980-2223.

Authors' Contributions: Work conceptualization: TE, JaF; statistical analysis: TE, JaF, MG, NS; study design and data acquisition: CL, MF, KUE, JuF, FK, PS and DCW. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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Table 1. Baseline characteristics stratified by the two study groups (ie, human insulin vs. analog insulin treatment).

	Human insulin	**Analog insulin**
N	733	713
Age at baseline (years)	68.6 (10.2)	64.7 (11.2)
Male sex (%)	439 (59.9)	425 (59.6)
Vintage (days)	164 (357)	187 (367)
BMI (kg/m²)	27.4 (5.1)	28.1 (5.6)
Albumin (g/l)	37.0 (5.3)	37.0 (4.9)
Calcium (mmol/l)	2.2 (0.2)	2.2 (0.2)
Hemoglobin (g/l)	108 (16)	109 (16)
Phosphate (mmol/l)	1.4 (0.5)	1.5 (0.4)
HbA1c (%) / (mmol/mol)	7.1 (1.5) / 54.1 (1.7)	7.4 (1.8) / 57.4 (1.9)
ESA dosage (U/week)	4255 (7597)	4820 (6578)
Comorbidities		
Atherosclerotic heart disease (%)	232 (32.1)	152 (21.3)
Congestive heart failure (%)	184 (25.4)	98 (13.8)
Chronic obstructive pulmonary disease (%)	63 (8.7)	42 (5.9)
Stroke (%)	136 (18.8)	56 (7.9)
Dysrhythmias (%)	107 (14.8)	59 (8.3)
Peripheral artery disease (%)	168 (23.2)	98 (13.8)
Country		
United Kingdom (%)	23 (3.1)	81 (11.4)
Italy (%)	10 (1.4)	27 (3.8)
Spain (%)	165 (22.5)	230 (32.3)
Portugal (%)	349 (47.6)	35 (4.9)
Hungary (%)	49 (6.7)	16 (2.2)
Czech Republic (%)	116 (15.8)	15 (2.1)
Turkey (%)	21 (2.9)	309 (43.3)
Insulin after commencing HD (%)	208 (28.4)	229 (32.1)

BMI, Body mass index; ESA, Erythropoiesis-stimulating agents; HbA1c, Glycated hemoglobin A1c; HD, Hemodialysis.

Data are presented as mean (standard deviation) for continuous measures, and N (percentage per insulin group) for categorical measures.

Table 2: Absolute and relative risks associated with analog insulin compared to the human insulin group and endpoint.

	Percent with event at 3 years (analog vs. human)	**Event Rate per 100 patient years (analog vs. human)**	**Crude analysis**	**Adjusted IPW analysis**
All-cause mortality	22.0 vs. 31.4	11.4 vs 15.6	0.73 (0.60 – 0.89)	0.81 (0.66 – 0.99)
MACE	26.8 vs. 35.9	16.1 vs 21.7	0.74 (0.62 – 0.89)	0.82 (0.68 – 0.98)
Coronary	9.0 vs 14.3	4.9 vs 7.9	0.62 (0.46 – 0.85)	0.74 (0.55 – 1.00)
Cerebral	7.2 vs 9.7	3.9 vs 5.0	0.77 (0.53 – 1.10)	0.90 (0.62 - 1.29)
Heart Failure/ Fluid Overload	6.0 vs 9.5	3.3 vs 5.0	0.65 (0.44 to 0.95)	0.81 (0.55 - 1.18)
Peripheral	5.9 vs 14.2	3.2 vs 7.8	0.41 (0.29 – 0.59)	0.45 (0.32 - 0.64)
Hospitalization	58.2 vs. 75.0	50.0 vs 73.2	0.70 (0.61 – 0.79)	0.76 (0.67 – 0.86)
Hypoglycemia	14.1 vs. 15.0	7.6 vs 6.5	1.18 (0.81 – 1.72)	1.169 (0.80 – 1.72)
CV mortality	9.6 vs. 14.8	4.9 vs 7.2	0.68 (0.50 – 0.92	0.73 (0.54 – 0.99)
Non-CV mortality	11.0 vs. 15.2	5.6 vs 7.4	0.76 (0.56 – 1.01)	0.83 (0.62 – 1.13)

CV, Cardiovascular; MACE, Major adverse cardiac events. All other abbreviations as indicated in Table 1.

Absolute risks, event rat, as well as weighted using inverse probability weighting (crude analysis) and multivariate (right column) hazard regression analysis adjusted for demography (BMI, albumin, phosphate, calcium, hemoglobin, HbA1c, ESA usage, time on dialysis) and comorbidities (ischemic heart disease, heart failure, chronic obstructive pulmonary disease, cerebrovascular disease, dysrhythmia, peripheral artery disease) using doubly adjusted inverse probability weighting (IPW). Hazard ratios and 95% confidence intervals are depicted for the analogue insulin group compared to the human insulin group (reference group).

Figure 1: Proportion of patients in each insulin group stratified by country of the dialysis facility. Human insulin is red, Analogue Insulin is teal. Countries are depicted by increasing gross domestic product per capita from left to right. Absolute numbers of patients included in the presented cohort is depicted on the y-axis.

Figure 2: Cumulative incidence function plots for the endpoints of all-cause mortality, cardiovascular (CV) mortality, non-CV mortality, MACE, all-cause hospitalization, and hypoglycemia (<3mmol/l, sampled on HD). Follow-up time is censored at 3 years by transplantation, loss to follow-up, transfer out of the dialysis facility, recovery of kidney function or change in dialysis modality. The competing event of mortality (non-CV mortality in the case of CV mortality) is displayed to the right. Human insulin is red, Analogue Insulin is teal.

Figure 3: Subgroup analyses for analogue insulin treatment compared to human insulin treatment (reference) according to age, body mass index (BMI), sex, and geographical region of the respective dialysis facility. Overall adjusted hazard ratios (circles) and 95% confidence intervals (lines) for analogue compared to human insulin are depicted in the bottom panels and are also shown in Table 2. In the four upper subgroup panels, black and grey circles/lines indicate the respective subgroups for the sensitivity analyses. All analyses were based on multivariable hazard regression analyses adjusted for demography, biochemical parameters (body mass index, albumin, phosphate, calcium, hemoglobin, glycated hemoglobin A1c, Erythropoiesis-stimulating agents usage, time on dialysis), and comorbidities (ischemic heart disease, heart failure, chronic obstructive pulmonary disease, cerebrovascular disease, dysrhythmia, peripheral artery disease) using doubly robust inverse probability weighting (IPW). MACE, Major adverse cardiac events.

Figure 4: Lowess smoothing plot of HbA1c values during the follow-up period stratified by use of Analogue and Human Insulin. Human insulin is red, Analogue Insulin is teal.