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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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 whether treatment with analog insulin compared with 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 (AROii) study with kidney failure commencing hemodialysis and type 2 diabetes being treated with insulin within 288 dialysis facilities between 2007 and 2009 across 7 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.

Outcome: All-cause mortality, major adverse cardiovascular events (MACE), 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 with human insulin.

Results: There were 713 insulin analog and 733 human insulin users. Significant variation in insulin type by country was observed. Comparing analog with human insulin at 3 years, the percentage of patients experiencing end points and adjusted hazard ratios (AHR) were 22.0% versus 31.4% (AHR, 0.808 [95% CI, 0.66-0.99], $P = 0.04$) for all-cause mortality, 26.8% versus 35.9% (AHR, 0.817 [95% CI, 0.68-0.98], $P = 0.03$) for MACE, and 58.2% versus 75.0% (AHR, 0.757 [95% CI, 0.67-0.86], $P < 0.001$) for hospitalization. Hypoglycemia was comparable between insulin types at 14.1% versus 15.0% (AHR, 1.169 [95% CI, 0.80-1.72], $P = 0.4$). 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, treatment with analog insulins was associated with better clinical outcomes when compared with human insulin.

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Diabetes is a major risk factor for developing chronic kidney disease (CKD) and is the leading cause of kidney failure in Western societies.[1] According to the International Diabetes Federation's *Diabetes Atlas*,[2] the number of patients with diabetes will continue to rise from currently about 537 million to 643 million in 2030. Importantly, nondiabetic patients with kidney failure have 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 kidney failure show much higher rates of hypoglycemic and hyperglycemic crises compared with high-risk populations with diabetes who do not have kidney failure. Poor glycemic control in kidney failure patients on HD[8] or before 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 kidney failure treated with exogenous insulin[11] and driving insulin dosage adjustments. Exogenous human insulin (ie, rapid and long acting) has several clinical shortcomings, including postprandial hyperglycemia followed by hypoglycemia and weight gain.[12] Consequently, rapid- and long-acting insulin analogs have been designed to better imitate the endogenous insulin response in healthy individuals.[12] Novel insulin analogs translate into better glycemic control[13] and lower glycemic variability[14] in the general population with diabetes. However, in clinical trials no differences in mortality and major adverse cardiac events (MACE) have been found in these patients when comparing analog and human insulins.[15-17]

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 1,446 people with kidney failure from 7 European countries who 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 3 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 a treatment leading to better outcomes for people with diabetes on dialysis.

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/kidney failure 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 whether analog insulin compared with human insulin is associated with different outcomes in this group, we performed analyses using causal inference techniques of a large multicenter cohort of incident HD patient[21] with type 2 diabetes from >250 Fresenius Medical Care (FMC) dialysis centers in 7 participating countries.

Methods

Cohort and Data

The Analyzing Data, Recognizing Excellence and Optimizing Outcomes II (AROii) cohort was a prospective observational cohort study of incident HD patients enrolled at 1 of the 312 Fresenius Medical Care (FMC) facilities across 15 European countries between 2007 and 2009. Although the original cohort study had follow-up observation until 2014, patients under follow-up at this time point were small. For the current analysis the follow-up period 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, the analysis was limited to the countries providing at least 10 HD patients with type 2 diabetes receiving insulin treatment.

Data on demography, comorbidity, laboratory, hospitalization, mortality, medications, and individual HD sessions were available. The presence of 6 comorbid conditions was recorded using *International Classification of Diseases, Tenth Revision* (ICD-10) codes from administrative data using existing schema (ischemic heart disease, congestive heart failure, cerebrovascular accident, peripheral artery disease, chronic obstructive pulmonary disease, and dysrhythmia).

Eligibility, Insulin Exposure, and Follow-up

Participants in AROii were assessed for eligibility throughout their follow-up observation. They were considered eligible if they were identified as having type 2 diabetes and were receiving either a human or analog insulin, with the 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 taking insulin before starting HD. If a patient developed diabetes after having already begun HD, the follow-up period would begin when the insulin was first prescribed. Patients who were switched between analog and human insulins during the follow up period were excluded.

Because ICD-10 coding defines individuals with diabetes as "Insulin Dependent" or "Non-Insulin Dependent" rather than as type 1 or 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] Analog 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 analog insulin type (Table S2). The follow-up period was 3 years, censored for transfer out of an FMC facility, transplantation, recovery of kidney function, or change in dialysis modality.

End Points

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 end points have the competing events of death while receiving HD, or the censoring events previously described. A hospitalization event was defined as an admission to hospital lasting at least 1 day. A MACE event was defined as hospitalization with the primary reason for admission corresponding to the ICD-10 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 (ie, level 2 hypoglycemia). Glucose measurements were commonly performed with blood to monitor HD and kidney failure 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 whether 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 and 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 end point models, predicted using these variables and the end points, was undertaken using predictive mean matching-generated 20 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 analog insulin prescription using baseline covariates: age (≤50, >50-60, >60-70, >70-80, >80); sex; 6 comorbid conditions (Table S5); levels of albumin (≤35, >35 g/L), phosphate (≤0.8, >0.8-1.5, >1.5 mmol/L), and calcium (≤2.1, >2.1-2.6, >2.6 mmol/L); hemoglobin (<100, 100-120, >120 g/L) and glycated hemoglobin (HbA_{1c}, ≤6%, >6-7, >7-8, >8-9, >9); erythropoiesis stimulating agents (because of their impact on red-cell turnover and therefore HbA_{1c}, <2,000, 2,000 to <6,000, 6,000-<12,000, ≥12,000 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 were converted into weights from the reciprocal of the probabilities estimated from the baseline covariates to generate a well-balanced pseudo population (Table S6). Stabilization of weights was not required (mean unstabilized weight, 1.001 ± 0.431 SD using all 20 datasets).

Comparing analog to human insulin, we report the rate in person-years and the absolute proportion of patients experiencing the end points of all-cause mortality, MACE, all-cause hospitalization, and hypoglycemia (<3 mmol/L) at 3 years using the weighted dataset. Finally, we

Table 1. Baseline Characteristics Stratified by the 2 Study Groups (Human Insulin Versus Analog Insulin Treatment)

	Human Insulin	Analog Insulin
No. of patients	733	713
Age at baseline, y	68.6 ± 10.2	64.7 ± 11.2
Male sex	439 (59.9%)	425 (59.6%)
Vintage, d	164 ± 357	187 ± 367
BMI, kg/m^2	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
HbA_{1c}, %/mmol/mol	7.1 ± 1.5 / 54.1 ± 1.7	7.4 ± 1.8 / 57.4 ± 1.9
ESA dosage, U/wk	4,255 ± 7,597	4,820 ± 6,578
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%)

Data are presented as mean ± SD for continuous measures and number (percentage per insulin group) for categorical measures. Abbreviations: BMI, body mass index; ESA, erythropoiesis-stimulating agents; HbA_{1c}, glycated hemoglobin A_{1c}; HD, hemodialysis.

performed adjusted Cox proportional regressions, reporting pooled estimates across the 20 imputed datasets. The inclusion of imputed adjustment variables in our second stage ensures that uncertainty around the imputed adjustment variables is accommodated in end point estimates and has the capacity to further reduce bias. In Table S7, we present the 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 noncardiovascular mortality analyses are reported separately. We further estimated end points stratified by age, sex, BMI (<30 vs ≥30 kg/m^2), geography (Central/Eastern Europe: Czech Republic, Hungary, and Turkey; Western Europe: United Kingdom, Italy, Portugal, and Spain), re-estimating the weights for these subpopulations (re-estimated weights reported in Table S8).

To explore whether 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 the other participating countries. To explore whether differences in outcomes could be explained by glycemic control, we present lowess smoothing plots of HbA_{1c} for the duration of the analysis, stratified by insulin type. All analyses were undertaken in R version 4.1 (R Project), 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 patients based on ICD-10 codes, of whom 1,899 were prescribed insulin before or while receiving HD. Of these, 239 were identified as type 1 diabetes using the administrative algorithm (Fig S1), and were therefore excluded from the analysis. A further 52 patients were removed because they were from countries providing fewer than 10 patients, along with 162 patients who received a mixture of human and analog insulins, leaving 1,446 patients recruited from 288 facilities across 7 countries for the present analysis, with a total of 2,855 patient-years of follow-up evaluation (1.97 years per patient). Insulin was commenced before or within 90 days of starting HD in 69.8% (1,009 patients). The study flow diagram is shown in Figure S2. Only a small proportion of patients (n = 75) were 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 analog group. Although use of the 2 insulins

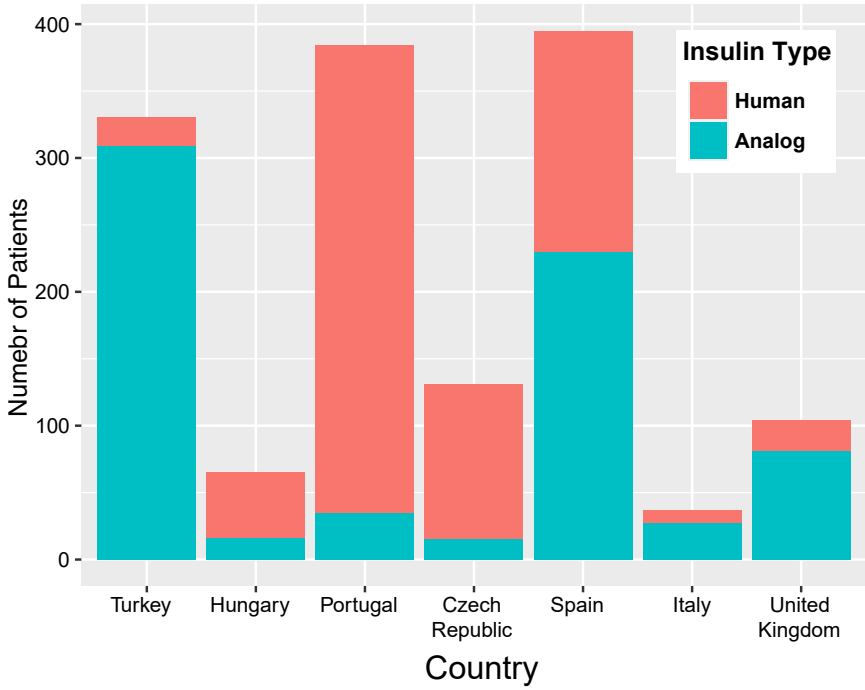

Figure 1. Proportion of patients in each insulin group stratified by country of the dialysis facility. Human insulin is red, and analog insulin is teal. Countries are depicted by increasing gross domestic product per capita from left to right. Absolute numbers of patients included in the presented cohort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

was approximately evenly split across the entire cohort, there was significant variation across the 7 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 Analog Versus Human Insulin and End Points

Within the 1,446 patients included in the adjusted analysis, there were 387 deaths (173 cardiovascular, 186 noncardiovascular, and 28 unknown), 965 first hospitalizations, 454 first MACE events, and 138 first hypoglycemic events (<3 mmol/L sampled on HD) over a median follow-up period of 27.7 months. Cumulative incidence function plots stratified by analog and human insulin are presented in Figure 2 with the proportions experiencing events in Table 2. Analog insulin was associated with superior event-free survival for the primary end points 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.

Multivariable adjustment for demography, biochemical parameters, and comorbidities using doubly adjusted IPW estimated the hazard ratios and 95% CI for all-cause mortality (HR, 0.808 [95% CI, 0.659-0.991], P = 0.04); MACE (HR, 0.817 [95% CI, 0.680-0.983], P = 0.03); hospitalization (HR, 0.757 [95% CI, 0.665-0.861], P < 0.001), and hypoglycemia (HR, 1.169 [95% CI, 0.796-1.718], P = 0.4) (Table 2). Cardiovascular and non-cardiovascular-specific mortality hazard ratios for analog versus human insulin were 0.734 [95% CI, 0.541-0.996]

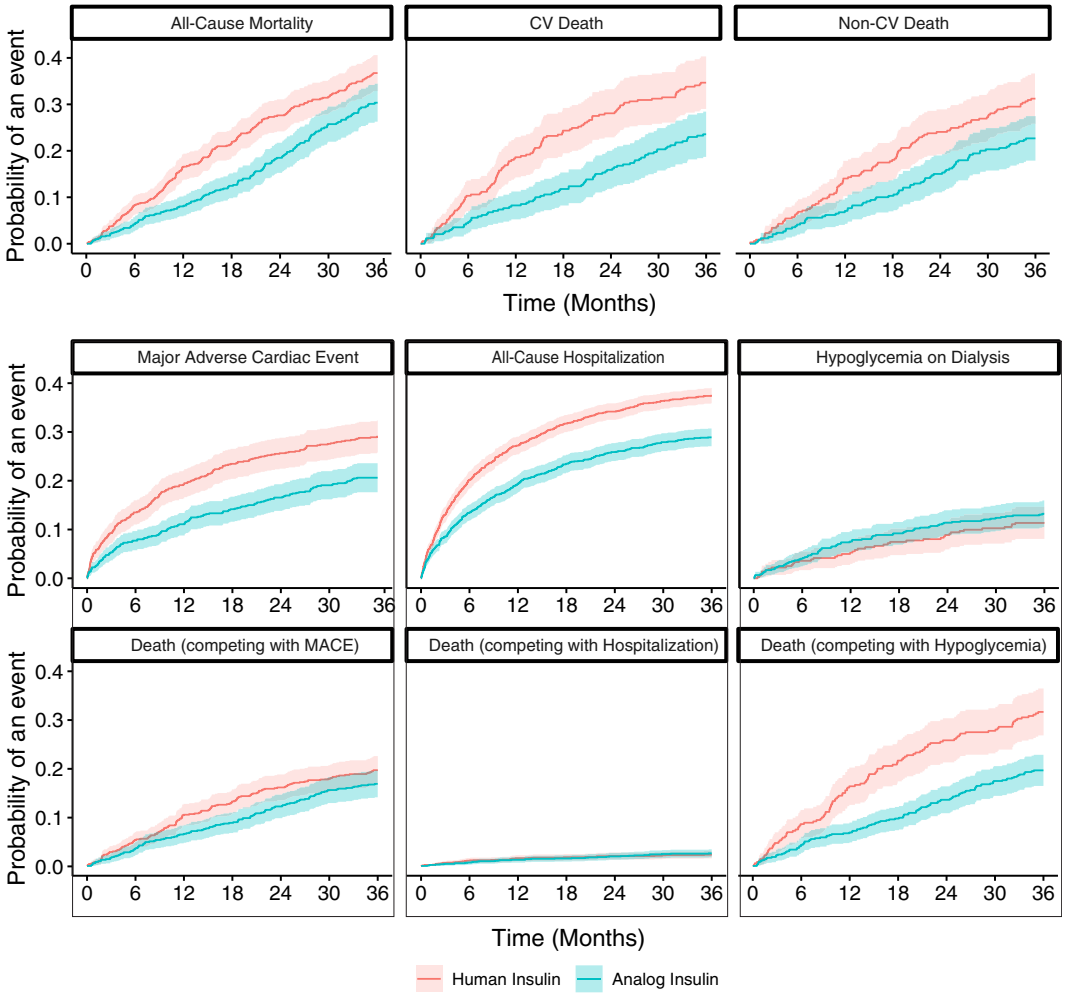

Figure 2. Cumulative incidence function plots for the end points of all-cause mortality, CV mortality, non-CV mortality, MACE, all-cause hospitalization, and hypoglycemia (<3 mmol/L, sampled on HD). Follow-up time is censored at 3 years by transplantation, loss to follow-up, transfer out of the dialysis 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, and analog insulin is teal. Abbreviations: CV, cardiovascular; HD, hemodialysis; MACE, major adverse cardiac events.

Table 2. Absolute and Relative Risks Associated With Analog Insulin Compared With the Human Insulin Group and End Point

	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 (0.44-0.95)	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)

Hazard ratios and 95% CI are depicted for the analog insulin group compared with the human insulin group (reference group). Absolute risks, event rate, as well as weighted using IPW (crude analysis) and multivariate (right column) hazard regression analysis adjusted for demography (body mass index, albumin, phosphate, calcium, hemoglobin, glycated hemoglobin A_{1c}, erythropoiesis-stimulating agent usage, time on dialysis) and comorbidities (ischemic heart disease, heart failure, chronic obstructive pulmonary disease, cerebrovascular disease, dysrhythmia, peripheral artery disease) using doubly adjusted IPW. Abbreviations: CV, cardiovascular; IPW, inverse probability weighting; MACE, major adverse cardiac events.

($P = 0.05$) and 0.834 [95% CI, 0.617-1.128] ($P = 0.2$) in the adjusted IPW analysis (Table 2). When the components of the MACE end point were analyzed separately (Table 2), the results remained similar in terms of effect strength and direction. The mean coefficient of variation of glucose levels measured on HD, in the countries performing it regularly, was 0.328 for the analog insulin group and 0.326 for the human insulin group (t test, $P = 0.9$), and the trajectory of HbA_{1c} in the 2 groups were not visually different (Fig 3).

Subgroup Analyses

Subgroup analyses showed a consistent direction of effect in favor of analog insulin for different subgroups of age, BMI, sex, and geographical region (Fig 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 analog insulin therapy is associated with lower all-cause mortality, MACE, and hospitalization compared with human insulin therapy, while level 2 hypoglycemia (<3.0 mmol/L) on HD and glycemic variability remained similar compared with human insulin.

Patients with kidney failure treated by HD have a shortened life span, with a difference of >25 years when

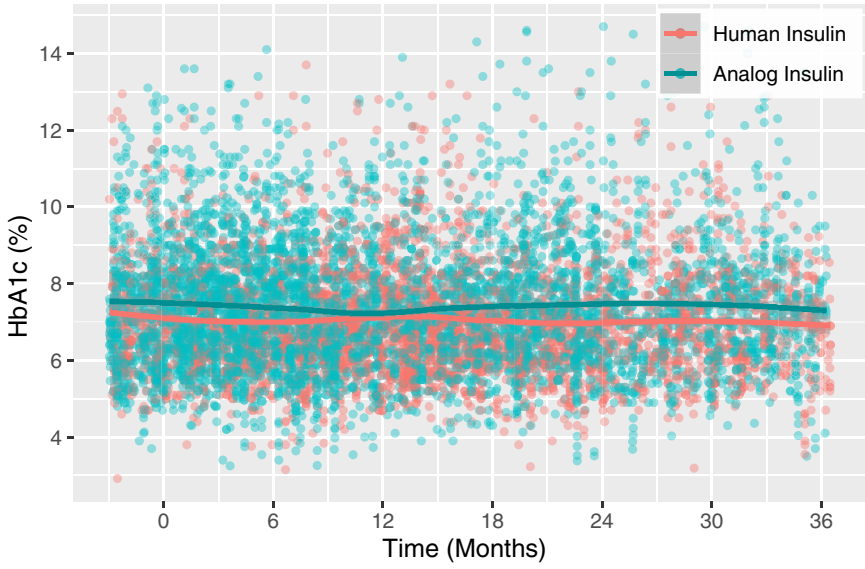

Figure 3. Lowess smoothing plot of HbA_{1c} values during the follow-up period stratified by use of analog and human insulin. Human insulin is red, and analog insulin is teal. Abbreviations: HbA_{1c}, glycated hemoglobin A_{1c}; MACE, major adverse cardiac events.

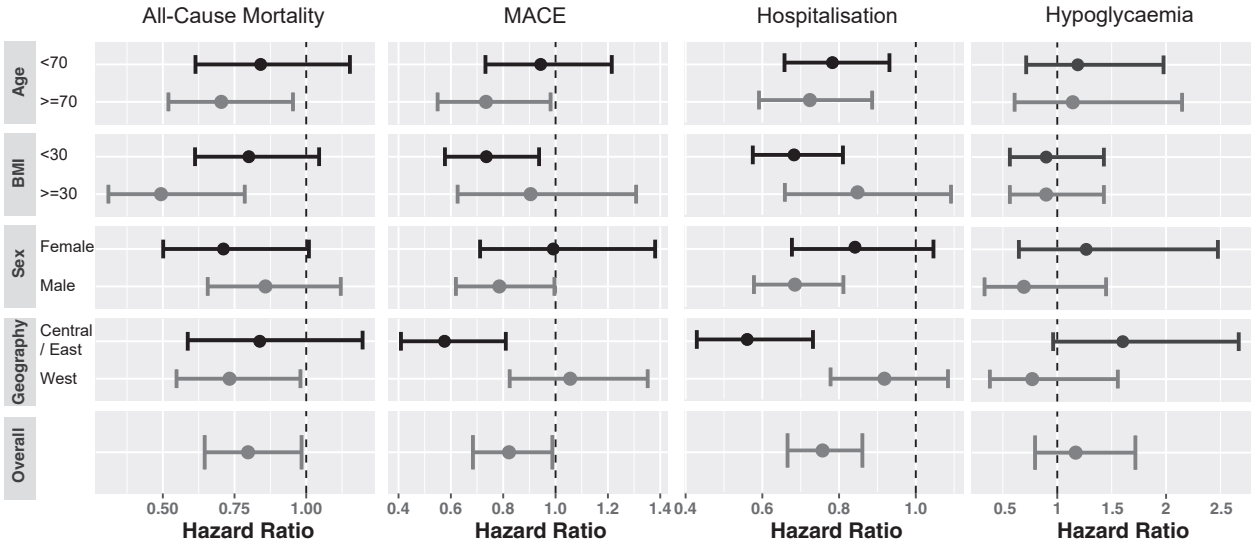

Figure 4. Subgroup analyses for analog insulin treatment compared with human insulin treatment (reference) according to age, BMI, sex, and geographical region of the respective dialysis facility. Overall adjusted hazard ratios (circles) and 95% CI (lines) for analog compared with human insulin are depicted in the bottom panels and are also shown in Table 2. In the 4 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 (BMI, albumin, phosphate, calcium, hemoglobin, glycated hemoglobin A_{1c}, erythropoiesis-stimulating agent usage, time on dialysis), and comorbidities (ischemic heart disease, heart failure, chronic obstructive pulmonary disease, cerebrovascular disease, dysrhythmia, peripheral artery disease) using doubly adjusted IPW. Abbreviations: BMI, body mass index; HbA_{1c}, glycated hemoglobin A_{1c}; IPW, inverse probability weighting; MACE, major adverse cardiac events.

compared with the general population.[1] In individuals with type 2 diabetes, kidney failure is associated with an excess mortality rate compared with individuals without kidney failure with type 2 diabetes.[29] Importantly, patients with type 2 diabetes on HD are excluded from most of the cardiorenal-protective glucose-lowering medications, including sodium-glucose cotransporter 2 (SGLT2) inhibitors,[30] and insulin therapy is the cornerstone of antihyperglycemic treatment in kidney failure.

In contrast with our findings in people with type 2 diabetes and kidney failure receiving HD, analog compared with human insulin treatment is not associated with differences in mortality and MACE outcomes in the general diabetic population.[15-17] Neugebauer et al[15] demonstrated similar rates of all-cause and cardiovascular mortality as well as MACE using a retrospective dataset from 4 US health care delivery systems comprising 127,600 adults with type 2 diabetes; however, the adjustment for time-varying HbA_{1c} 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 analog and human insulin, similar to a recent Cochrane review.[16] No trials have been designed to investigate the long-term effects (ie, 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/kidney failure) other factors and covariates may counterbalance any potential differences between analog versus human insulin—for instance, concomitant use of other (cardiorenal) protective glucose-lowering and/or lipid-lowering treatment. Notably, because 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 analogs could potentially explain the improved outcome of patients on analog insulins in our cohort. A recent meta-analysis in individuals with type 1 diabetes showed that analog insulin therapy was associated with lower total, nocturnal, and severe hypoglycemia risk, as well as reduced postprandial glucose and HbA_{1c}.[31] In type 2 diabetes, long-acting analogs do not result in insulin peaks compared with long-acting human insulins (ie, neutral protamine Hagedorn insulin), thereby reducing hypoglycemia risk.[32] In contrast, short-acting analogs induce a faster and higher peak plasma insulin concentration in the first hour after injection compared with human short-acting insulin, thereby reducing the adverse postprandial glucose peak.[33] Both long- and short-acting analogs, therefore, could significantly reduce glycemic variability, which has been linked to mortality in people on HD,[34] without necessarily modifying HbA_{1c}.

Two recent retrospective population-based cohort studies from the United Kingdom and Taiwan have also reported beneficial effects of (long-acting) analog insulin with respect to cardiovascular outcomes as well as hypoglycemic risk, supporting our findings in this more vulnerable cohort.[35,36]

The cumulative incidence curves for mortality, MACE, and hospitalization outcome separated as early as the first months of follow-up (ie, 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 (Fig 2) in our cohort. In addition, some patients already started analog insulins before being included in our study, and potential beneficial treatment effects of analog insulins could have accumulated before 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, and increased costs of analog 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 (eg, basal insulin-only vs basal-bolus insulin regimen) or different types of analogs (eg, 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.

Our study's strengths include its potentially high relevance for daily practice because there is an unmet need to improve the prognosis of individuals with type 2 diabetes and kidney failure. Furthermore, we have applied sophisticated statistical analyses with robust adjustment for multiple variables using a validated clinical database, and we analyzed many patients using well-defined outcomes. Prospective, adequately designed and powered clinical trials should investigate whether switching from human insulin to analog insulin improves patient-relevant outcomes in people with kidney failure and explore the cost-effectiveness of this intervention.

In conclusion, in a large, multinational cohort of HD patients with type 2 diabetes, analog compared with human insulin was associated with better clinical outcomes, although hypoglycemia rates were increased. Analog 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 analog or human insulins, as well as premixed insulins.

Table S3: Overview of the 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 2 study groups (ie, human insulin vs analog insulin treatment).

Table S6: Baseline characteristics stratified by the 2 study groups (ie, human insulin vs analog 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 analog and human insulin users by country.

Article Information

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