Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.
**Methods 1 - Cohort Construction**

We searched the electronic health records and administrative databases of the HP, KPCO, KPNC, KPSC health plans to identify all diabetes patients between 1/1/2000 and 12/31/2013 with a first insulin dispensing between 1/1/2005 and 12/31/2013. The algorithm used to identify diabetes patients is described below (second bullet). The date of first insulin dispensing is referred to as the index date. Each patient who met all of the following criteria was included in the main study cohort:

- age on index date ≥ 21 and ≤ 89
- diabetes recognition occurred before or on index date where the diabetes recognition date was defined from the patient’s diagnoses from inpatient, ambulatory, laboratory, and pharmacy encounters. Specifically, diabetes recognition was defined as the earlier of one inpatient diagnosis (ICD-9-CM 250.x, 357.2, 366.41, 362.01-362.07) or any combination of two of the following events occurring within a 24-month period of time, using the date of the first event in the pair as the identification date: 1) A1C > 6.5% (48 mmol/mol); 2) fasting plasma glucose > 126 mg/dl (7.0 mmol/L); 3) random plasma glucose > 200 mg/dl (11.1 mmol/L); 4) an outpatient diagnosis code (same codes as inpatient); 5) any anti-hyperglycemic medication dispense. For example, an individual with an A1C of 7.5% (57 mmol/mol) followed by an outpatient diagnosis of diabetes would be identified with diabetes on the (earlier) date of the A1C, with a laboratory result as the primary source. When the two events used for identification came from the same source (e.g., two outpatient diagnoses), they were required to occur on separate dates, but no more than 24-months apart. Note the following exception: two dispensings of metformin, thiazolidinediones, or liraglutide – with no other indication of diabetes – was not counted because these agents could be used for diabetes prevention, weight loss or to treat polycystic ovarian syndrome. Events that were identified during a pregnancy (within 270 days prior to a delivery) were excluded from consideration
- minimum of 12 months of health plan enrollment before index date and allowing for multiple gaps not exceeding 90 days combined
- minimum of 12 months of drug coverage before index date and allowing for multiple gaps not exceeding 90 days combined
- not pregnant on index date
- no evidence of bariatric surgery in the 2 years before the index date, i.e., no record of the following ICD-9 procedure and CPT-4 codes: 43.89, 44.31, 44.38, 44.39, 44.68, 44.69, 44.95; 43633, 43644, 43645, 43659, 43770, 43775, 43842, 43843, 43844, 43845, 43846, 43847
- no evidence of end stage renal disease in the 2 years before the index date, i.e., no record of the following ICD-9 diagnosis, ICD-9 procedure, and CPT-4 codes (kidney transplant): v42.0, 996.81; 55.6, 55.61, 55.69; 50360, 50365, 50380 and most recent GFR laboratory result (if any) ≥ 15 and no record of 2 or more of the following ICD-9 diagnosis, ICD-9 procedure, and CPT-4 codes dated >90 days apart as primary or secondary diagnosis (dialysis): 585.6, 458.21, v45.1, v45.11, v56, v56.x, v56.2, v56.8; 39.95, 54.98; 90921, 90925, 90935-90999
- no evidence of a stage 4 cancer diagnosis in the 2 years before the index date, i.e., no record of the following ICD-9 diagnosis codes 197.x, 198.x, 199.x
- no evidence of hospice or palliative care in the 2 years before the index date, i.e., no record of an hospice encounter and no record of the ICD-9 diagnosis code v66.7 and no record of the CPT code 99377 and 99378
- at least one A1c laboratory measurement recorded in the 2 years before the index date
- insulins dispensed on the index date do not include animal or inhaled insulins
- diabetes of type 2 defined by the following ratio being strictly lower than 50%: the number of ICD-9 diagnosis codes 250.x1 and 250.x3 (type 1) in the 2 years before the index date divided by the sum of this number and the number of ICD-9 codes 250.x0 and 250.x2 (type 2) in the 2 years before the index date. If this ratio is not defined (i.e., denominator is 0), the diabetes type is unknown and the patient excluded from the study cohort.

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In addition to these criteria above, KPCO patients living outside the Denver/Boulder area were excluded due to incomplete data capture.

**eMethods 2 - Data Structure and Notation**

All analyses in this report are based on analytic datasets constructed with the MSMstructure SAS macro\(^1\) to coarsen daily EHR data using the 90-day unit of time, i.e., time-dependent variables are updated every 90 days in the resulting analytic datasets. More specifically, for each of the five failure time outcomes considered (eTable 1), a separate analytic dataset is constructed by collecting the realizations of the random variables described below for all patients in the main or CVD study cohort.

Follow-up time (expressed in 90-day units) is denoted by \(t\) and, by convention, the first 90 days of follow-up are denoted by \(t = 0\). The time when the patient’s follow-up ends is denoted by \(\bar{T}\) and is defined as the earliest of the time to failure denoted by \(T\) or the time to a right-censoring event denoted by \(C\). When a patient is right-censored, i.e., \(C < T\), the type of right-censoring event experienced by the patient is recorded and denoted by \(\Gamma\) with possible values 1-7 to represent the administrative end of study, disenrollment from the health plan, start of a pregnancy, switch in therapy type (i.e., crossover from human-only to analog-containing therapy or vice versa), initiation of a nonstandard insulin (i.e., inhaled or animal insulin), interruption of insulin therapy, or death, respectively. The indicator that the end of follow-up is due to the occurrence of a failure event is denoted by \(\Delta = I(T \leq C)\), i.e., \(\Delta = 1\) implies that \(\bar{T} = T\) and \(\Delta = 0\) implies that \(\bar{T} = C\). The indicator that the patient initiated analog-containing insulin therapy on the index date is represented by the binary variable \(A_{1}(0)\) (i.e., \(A_{1}(0) = 0\) indicates exposure to human-only insulin therapy). The indicator of the patient’s right-censored status at time \(t\) is denoted by \(A_{2}(t)\). We thus have \(A_{2}(t) = 0\) for \(t = 0, \ldots, \bar{T} - 1\) when \(\bar{T} \geq 1\) and \(A_{2}(\bar{T}) = 1 - \Delta\). The exposure variable denoted by \(A(t)\) is defined by \(A(0) = (A_{1}(0), A_{2}(0))\) and \(A(t) = A_{2}(t)\) for \(t > 0\). At each time point \(t = 0, \ldots, \bar{T}\), covariates such as A1c measurements (eTables 2-3) are denoted by a component \(L_{j}(t)\) of the random vector \(L(t)\) and defined from measurements that occur before the exposure at time \(t\), \(A(t)\), or are otherwise assumed not to be affected by the exposures at time \(t\) or thereafter, \((A(t), A(t + 1), \ldots)\). If no such measurements were collected, each variable \(L_{j}(t)\) is defined by convention using last observed value carried forward at \(t > 0\). If no baseline measurements were collected for a continuous variable in \(L(0)\), the variable is defined by convention as the median of the baseline values from patients with observed measurements at \(t = 0\). For categorical variables in \(L(0)\), a separate level is defined to encode missing baseline measurements. For each time-independent or time-dependent covariate \(L_{j}\) with at least one missing measurement (at baseline or at \(t > 0\)), an indicator of missing covariate measurement at time \(t\) is created and included as a distinct variable (e.g., to encode intensity of clinical monitoring) in the random vector \(L(t)\) for all time points \(t\). In addition, the vector of covariates \(L(t)\) at time \(t\) include an outcome measurement denoted by \(Y(t)\), i.e., \(Y(t) \in L(t)\) for \(t = 0, \ldots, \bar{T}\). For each time point \(t = 1, \ldots, \bar{T} + 1\), the outcome is the indicator of past failure, i.e., \(Y(t) = I(T \leq t - 1)\) and \(Y(0) = 0\) by convention. By definition, the outcome is thus 0 for \(t = 0, \ldots, \bar{T}\), not observed at \(t = \bar{T} + 1\) if \(\Delta = 0\) and, 1 at \(t = \bar{T} + 1\) if \(\Delta = 1\).

In short, the observed data in each analytic dataset are realizations of \(n\) copies \(O\), of the random process \(O = (\hat{T}, \Delta, (1 - \Delta)\Gamma, \hat{L}(\hat{T}), \hat{A}(\hat{T}), \hat{\Delta}Y(\hat{T} + 1))\) where \(n = 127,600\) in each of the four analytic datasets to evaluate AMI, CHF, CVA, all-cause mortality and \(n = 95,300\) in the analytic dataset to evaluate CVD mortality. In the analyses of each dataset, we assumed\(^2\) that the random variables \(O\) are independent and identically distributed.

To simplify expressions below, we use the overbar notation \(\bar{\cdot}\) to denote the history of a variable \(\cdot\) from baseline to time \(t\) (e.g., \(\bar{A}(t) = (A(0), A(1), \ldots, A(t))\)) and, by convention, \(L(t)\) and \(A(t)\) are nil when \(t < 0\).

**eMethods 3 - Causal Estimands and Inverse Probability Estimator**

The following two working\(^3\) logistic marginal structural models (MSMs) for discrete-time counterfactual hazards, \(P(Y_{\bar{a}(t)}(t + 1) = 1 \mid Y_{\bar{a}(t-1)}(t) = 0)\), were considered:

- a simple MSM whose parameterization mimics a common modeling practice that assumes constant hazard ratios over time (i.e., a model based on the proportionality assumption):

\[
m_{1}(t, a_{1}(0) \mid \beta) = \left(1 + \exp \left(-\left(\beta^{0} I(a_{1}(0) = 1) + \sum_{j=1}^{10} \beta^{j} I(t = j - 1)\right)\right)\right)^{-1}
\]

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• a saturated MSM whose parameterization permits hazard ratios to change over time:

\[ m_2(t, a_1(0) \mid \beta) = \left(1 + \exp \left(-\left(\sum_{j=1}^{10} \sum_{k=0}^{1} \beta_{jk} I(t = j - 1, a_1(0) = k)\right)\right)\right)^{-1} \]

for \( t = 0, \ldots, 9 \) and \( \bar{a}(t) = \bar{a}^0(t), \bar{a}^1(t) \) where, for each MSM, the collection of its coefficients is denoted by \( \beta \) and where \( \bar{a}^0(t) = ((0,0),0,\ldots,0) \) represents continuous exposure to human-only insulin therapy and \( \bar{a}^1(t) = ((1,0),0,\ldots,0) \) represents continuous exposure to analog-containing insulin therapy.

The standard bounded and stabilized IPW estimator approach to fit each MSM was implemented in this report with the following choice of numerators (stabilizing factor) for the IP weights assigned to the person-time outcomes contributing to the weighted regression: \( \prod_{j=0}^{t} P_n(A(j) = a_k^j(j) \mid A(j-1) = \bar{a}^k(j-1)) \) with \( k = 0, 1 \) and \( t = 0, \ldots, 9 \) where each factor \( P_n \) denotes a sample mean. The resulting IPW estimator of the MSM coefficient \( \beta \) is denoted by \( \beta_n \) and define the various effect measures reported below.

The first MSM fit provided a single effect measure estimate \( \exp(\beta_0^n) \) corresponding with an estimate of the constant causal hazard ratio (HR) \( P(Y_{\bar{a}^1(t)}(t + 1) = 1) / P(Y_{\bar{a}^0(t)}(t + 1) = 1) \) under the proportionality assumption and rare event assumption. The second MSM fit was mapped into estimates of the counterfactual cumulative risks \( P(Y_{\bar{a}^k(t)}(t + 1) = 1) \) (equivalently, the counterfactual survival probability \( P(T_{\bar{a}^k(t)} > t) = 1 - P(Y_{\bar{a}^k(t)}(t + 1) = 1) \)) as follows for \( t = 0, \ldots, 9 \) and \( k = 0, 1 \):

\[ P_n(Y_{\bar{a}^k(t)}(t + 1) = 1) = 1 - \prod_{j=0}^{t} \left(1 - m_2(j, k \mid \beta_n)\right). \]

These estimates of counterfactual cumulative risks defined three effect measure estimates:

• the difference between the areas under the two discrete-time survival curves (AUC):

\[ \sum_{j=0}^{9} \left(P_n(Y_{\bar{a}^1(j)}(j + 1) = 1) - P_n(Y_{\bar{a}^0(j)}(j + 1) = 1)\right) \]

• the risk difference (RD) at 1 year: \( P_n(Y_{\bar{a}^1(3)}(4) = 1) - P_n(Y_{\bar{a}^0(3)}(4) = 1) \)

• the risk difference (RD) at 2 years: \( P_n(Y_{\bar{a}^1(7)}(8) = 1) - P_n(Y_{\bar{a}^0(7)}(8) = 1) \).

Inferences for the AUC and RD effect measures were derived from prior work\(^5\) based on the delta method and the influence curve of the IPW estimator \( \beta_n \).

**eMethods 4 - Denominator of the Inverse Probability Weights**

The conditional probabilities \( P(A(t) = a^k(t) \mid \bar{L}(t), \bar{Y}(t) = 0, \bar{A}(t-1) = \bar{a}^k(t-1)) \) for \( t = 0, \ldots, 9 \) and \( k = 0, 1 \) that define the denominators of the IP weights used to fit the MSMs described above can be factorized based on the following 10 propensity scores (PS) for:

• baseline initiation of analog-containing insulin therapy denoted by \( \mu_1(0) \):

\[ P(A_1(0) = 1 \mid L(0)) \]

• right-censoring due to administrative end of study denoted by \( \mu_2(t) \):

\[ P\left(I(A_2(t) = 1, \Gamma = 1) = 1 \mid \bar{L}(t), \bar{Y}(t) = 0, A_1(0), \bar{A}(t-1) = 0\right) \]

• right-censoring due to disenrollment from the health plan denoted by \( \mu_3(t) \):

\[ P\left(I(A_2(t) = 1, \Gamma = 2) = 1 \mid \bar{L}(t), \bar{Y}(t) = 0, A_1(0), \bar{A}(t-1) = 0, I(A_2(t) = 1, \Gamma = 1) = 0\right) \]
• right-censoring due to start of pregnancy denoted by $\mu_4(t)$:

$$P\left(I\left(A_2(t) = 1, \Gamma = 3\right) = 1 \mid \bar{L}(t), L_\varphi(0) = 1, \bar{Y}(t) = 0, A_1(0), \bar{A}_2(t - 1) = 0, I\left(A_2(t) = 1, \Gamma \in \{1, 2\}\right) = 0\right) = 0$$

where $L_\varphi(0)$ denotes the indicator that the patient is female

• right-censoring due to crossover from analog-containing to human-only insulin therapy denoted by $\mu_5(t)$:

$$P\left(I\left(A_2(t) = 1, \Gamma = 4\right) = 1 \mid \bar{L}(t), \bar{Y}(t) = 0, A_1(0) = 1, \bar{A}_2(t - 1) = 0, I\left(A_2(t) = 1, \Gamma \in \{1, 2, 3\}\right) = 0\right) = 0$$

• right-censoring due to crossover from human-only to analog-containing insulin therapy denoted by $\mu_6(t)$:

$$P\left(I\left(A_2(t) = 1, \Gamma = 4\right) = 1 \mid \bar{L}(t), \bar{Y}(t) = 0, A_1(0) = 0, \bar{A}_2(t - 1) = 0, I\left(A_2(t) = 1, \Gamma \in \{1, 2, 3\}\right) = 0\right) = 0$$

• right-censoring due to initiation of a non-standard insulins (animal or inhaled) denoted by $\mu_7(t)$:

$$P\left(I\left(A_2(t) = 1, \Gamma = 5\right) = 1 \mid \bar{L}(t), \bar{Y}(t) = 0, A_1(0), \bar{A}_2(t - 1) = 0, I\left(A_2(t) = 1, \Gamma \in \{1, \ldots, 4\}\right) = 0\right) = 0$$

• right-censoring due to early (i.e., at $t = 2$) interruption of insulin therapy denoted by $\mu_8(2)$:

$$P\left(I\left(A_2(t) = 1, \Gamma = 6\right) = 1 \mid \bar{L}(2), \bar{Y}(2) = 0, A_1(0), \bar{A}_2(1) = 0, I\left(A_2(t) = 1, \Gamma \in \{1, \ldots, 5\}\right) = 0\right) = 0$$

• right-censoring due to late (i.e., at $t > 2$) interruption of insulin therapy denoted by $\mu_9(t)$:

$$P\left(I\left(A_2(t) = 1, \Gamma = 6\right) = 1 \mid \bar{L}(t), \bar{Y}(t) = 0, A_1(0), \bar{A}_2(t - 1) = 0, I\left(A_2(t) = 1, \Gamma \in \{1, \ldots, 5\}\right) = 0\right) = 0$$

• right-censoring due to death denoted by $\mu_{10}(t)$:

$$P\left(I\left(A_2(t) = 1, \Gamma = 7\right) = 1 \mid \bar{L}(t), \bar{Y}(t) = 0, A_1(0), \bar{A}_2(t - 1) = 0, I\left(A_2(t) = 1, \Gamma \in \{1, \ldots, 6\}\right) = 0\right).$$

We note that the last PS above is not considered to define the IP weights in the analyses that evaluate all-cause mortality because death is then the failure outcome of interest (i.e., there is no right-censoring due to death). For the AMI, CHF, CVA, and CVD mortality outcomes, we constructed the denominators of the IP weights for all outcomes contributing to the MSM fits as follows for $t = 0, \ldots, 9$:

$$\mu_1(0)^{A_1(0)}(1 - \mu_1(0))^{1 - A_1(0)} \prod_{j=0}^{9} (1 - \mu_2(j))(1 - \mu_3(j))(1 - \mu_4(j))^{L_\varphi(0)}(1 - \mu_5(j))^{A_1(0)}(1 - \mu_6(j))^{1 - A_1(0)}(1 - \mu_7(j))(1 - \mu_8(2)) I(j=2)(1 - \mu_9(j)) I(j>2)(1 - \mu_{10}(j)).$$

Each of the first three approaches considered for estimating these denominators of the IP weights consists in fitting a separate logistic model for each of the the 10 PS $\mu_j(t)$ just described. The three approaches only differ by the set of covariates that define each of the main terms included in each logistic model. We describe these sets in the next section.
Methods 5 - Standard Propensity Score Estimation with Three Covariate Adjustment Sets

In the first approach implemented to estimate the denominators of the IP weights, the main terms included in a given PS logistic model were those associated with covariates presumed to impact both failure and the PS outcome as indicated in eTables 4-5. For instance, in the analyses of CHF, the PS logistic model for baseline initiation of analog-containing (versus human-only) insulin therapy included main terms for all covariates in these tables where a value of 1 is found in both the $\mu_1(0)$ and CHF columns. For the time-dependent covariates selected based on this rationale, only main terms for their current values $L(t)$ were included in the PS logistic models, i.e., no main terms for other summary measures of the covariate histories were considered (e.g., latest change in value $L(t)−L(t−1)$ or a lagged value $L(t−1)$). In addition, all PS logistic models except for non-standard insulin initiation included main terms for the patient’s age at index date and the PS logistic model for $\mu_1(0)$ also included main terms for and interaction terms between the dummy variables that encode health plan membership (i.e., HP, KPCO, KPNC, or KPSC) and the index date year. All PS logistic models fitted with pooled data over time (i.e., $\mu_j(t)$ for $j = 2, \ldots, 7, 9, 10$) also included main terms for time $t$ (expressed in 90-day intervals). In addition, except for the PS logistic model for $\mu_1(0)$, all other PS models included a main term for the baseline insulin therapy $A_1(0)$. For the PS logistic models for administrative end of study and start of pregnancy, only main terms for age at index, $t$, and $A_1(0)$ were included in the models. For the PS logistic model for the initiation of non-standard insulins, only main terms for $t$ and $A_1(0)$ were included in the model because <5 patients initiated non-standard insulins which limited the number of covariate that could be considered. All continuous variables considered by the various PS logistic models were discretized using the cutoffs given in eTable 6 and main terms for the resulting dummy variables (for the non-reference level) were included in the models. eTable 7 provides an example of the logistic model fit for $\mu_1(t)$ based on the PS estimation approach 1.

The second approach implemented to estimate the denominators of the IP weights followed the same principles with the difference that the main terms included in a given PS logistic model (including for start of pregnancy and administrative end of study) were those associated with covariates presumed to, at least, impact failure as indicated in eTables 4-5. However, for the PS logistic model for the initiation of non-standard insulins, only main terms for $t$ and $A_1(0)$ were included in the model because <5 patients initiated non-standard insulins which limited the number of covariate that could be considered. All other modeling decisions were identical to those of the first approach described above. eTables 8-9 provide an example of the logistic model fit for $\mu_5(t)$ based on the PS estimation approach 2.

The third approach implemented to estimate the denominators of the IP weights followed the same principles with the difference that the main terms included in a given PS logistic model were those associated with the covariates presumed to impact either failure or the PS outcome as indicated in eTables 4-5. The PS logistic models for the start of pregnancy and administrative end of study included main terms for all covariates presumed to affect failure. However, for the PS logistic model for the initiation of non-standard insulins, only main terms for $t$ and $A_1(0)$ were included in the model because <5 patients initiated non-standard insulins which limited the number of covariate that could be considered. All other modeling decisions were identical to those of the first approach described above. eTables 10-11 provide an example of the logistic model fit for $\mu_5(t)$ based on the PS estimation approach 3.

Thus, the three sets of variables that define the main terms included in any given PS logistic model according to the three approaches just described are nested and of increasing size.

Methods 6 - Data-adaptive Propensity Score Estimation

In the fourth approach implemented to estimate the denominators of the IP weights, a separate super learner was used to estimate each of the 10 PS $\mu_j(t)$ instead of a separate logistic model (as done in the first three approaches). Each super learner was constructed based on 10-fold cross-validation and three learners corresponding with the same three logistic models considered in the first three PS estimation approaches described above. eTable 12 provides an example of the super learner fit for $\mu_5(t)$ based on the PS estimation approach 4.

Methods 7 - Results

eTable 13 describes the proportions of patients initiating HI versus AI therapy by site and year of study entry for patients in the main cohort. This table indicates that the great majority of patients from site 4 were first prescribed AI with little fluctuation over the years of the study. This is in contrast to the other 3 sites where most patients were first prescribed HI with relatively little temporal fluctuation at sites 2 and 3 and more temporal fluctuation at site 1 in insulin prescription patterns over the years of the study. Results from eTable 13 motivated the conduct of two sets of sensitivity analyses using, first, only the subset of patients from sites 1-3 (125,257), and second, only the subset of

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The distributions of follow-up times by exposure regimen for each of the five primary analyses are described in eTables 14-28.

Results of all primary and sensitivity analyses implemented with the four PS estimation approaches described above along with their corresponding unadjusted analyses (i.e., same models fitted without weights) are displayed in eTables 29, 30, 31, 32, and 33 for AMI, CHF, CVA, CVD-mortality, and all-cause mortality, respectively. Inference for the hazard ratio is given in the column “HR” and derived from the MSM fit that assumes constant hazard ratios over time (proportionality assumption). Inference in the “AUC”, “RD1”, and “RD2” columns are derived from the same saturated MSM fit. The “AUC” column contains the p-value from the statistical test that the area between the survival curves is equal to 0. The “RD1” and “RD2” columns provide inferences for the cumulative risk differences at 1 and 2 years (i.e., 4 and 8 quarters) after the index date. 95% confidence intervals for the HR and RDs are given in between squared brackets, standard errors are given by “SE”, and the p-values of the statistical tests that HR=1/RD=0 are given by “p”. We note that p-values were not adjusted for multiple testing. The crude (i.e., unadjusted) and SL-based IPW estimates of the counterfactual survival curves associated with the AUC p-values given in the eTables are displayed in eFigures 1-5. Summary statistics for the inverse probability weights involved in all primary and sensitivity analyses are displayed in eTables 34, 35, 36, 37, and 38 for AMI, CHF, CVA, CVD-mortality, and all-cause mortality, respectively.

Null findings from the primary PP analyses are generally supported by the adjusted estimates from sensitivity PP analyses. CHF results from the site 1 sensitivity analyses based on PS estimation with logistic models using covariate sets 2 and 3 and data-adaptive PS estimation with SL provided the greatest statistical evidence of a potential difference between the two exposure regimens considered and suggest a potential beneficial effect of AI against CHF, but not all cause mortality, CVD, MI, or CVA.
**eTable 1: Sources of Data and Codes Used to Ascertain Major Cardiovascular Events and Mortality.**

| Event                                                                 | ICD-9-CM Codes                      | Source                                                                 |
|----------------------------------------------------------------------|-------------------------------------|------------------------------------------------------------------------|
| **Fatal or Nonfatal** **Myocardial Infarction** *(including Acute Coronary Syndrome)* | ICD-9-CM codes : 410.xx             | Inpatient hospital discharges (principle discharge diagnosis)          |
| **Fatal or Nonfatal Stroke** *Ischemic stroke Hemorrhagic stroke*    | ICD-9-CM codes : 430.xx, 431.xx, 433.x1, 434.x1 | Inpatient hospital discharges (principle discharge diagnosis)          |
| **Hospitalization for Heart Failure** *(discharged either alive or deceased)* | ICD-9-CM codes: 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.xx | Inpatient hospital discharges (principle discharge diagnosis)          |
| **Cardiovascular Mortality**                                        | ICD9/ICD10 groups: CHD,HF: 50,51,52,53,54,55,58,59,60 CeVD: 61 PAD/Arteriosclerosis: 62,63 | Social Security Admin; National Death Index; State Death Records; Tumor Registry data; Encounter data; Patient data; Membership data |
| **Overall Mortality**                                               | --                                  | Social Security Admin; National Death Index; State Death Records; Tumor Registry data; Encounter data; Patient data; Membership data |

CHD: coronary heart disease; HF: heart failure; CeVD: cerebrovascular disease; PAD: peripheral arterial disease.
eTable 2: Part I of II - Brief description of all attributes ($L$) in the covariate adjustment sets.

| Covariate handle | Brief covariate definition |
|------------------|---------------------------|
| afib             | atrial fibrillation       |
| age.at.index     | age at index date         |
| alcoholabuse     | alcohol abuse             |
| anemia           | anemia                    |
| anticoag         | anticoagulant medication  |
| anxiety          | anxiety                   |
| asthma           | asthma                    |
| bariatric        | bariatric surgery         |
| bipolar          | bipolar affective disorder|
| bmi              | body mass index (Kg/m²)   |
| cabg             | coronary artery bypass graft|
| cad              | coronary artery disease   |
| cancer           | cancer other than non-melanoma skin cancer|
| census.hsgrad    | high school graduate      |
| census.medhhincome | median household income  |
| cevd             | cerebrovascular disease   |
| chf              | congestive heart failure  |
| chf.event        | CHF hospitalization       |
| ckd              | chronic kidney disease    |
| composite.protein| urine microalbumin creatinine ratio |
| connective       | vasculitis/connective tissue disease |
| copd             | chronic obstructive lung disease |
| dementia         | dementia                  |
| depression       | depression                |
| diastolic        | diastolic blood pressure  |
| dpp4             | DPP-4 class of glucose-lowering medication |
| drugabuse.alt    | substance abuse disorder (other than alcohol) |
| drugcount        | total number of prescription medications |
| early.adopter    | use of DPP-4, GLT-1, SGLTs within 5 years from FDA approval |
| elixhauser       | Elixhauser comorbidity score |
| flag.incident    | incident diabetes (diabetes recognition date $\geq 18$ months since health plan enrollment) |
| gender           | gender                    |
| gfr              | glomerular filtration rate cc/min/2.72m² |
| glp1             | GLP-1 agonist glucose lowering medication |
| hdl              | high-density lipoprotein cholesterol |
| hgba1c           | hemoglobin A1c value (%)  |
**eTable 3: Part II of II - Brief description of all attributes \( (L) \) in the covariate adjustment sets.**

| Covariate handle | Brief covariate definition |
|------------------|----------------------------|
| hiv              | HIV infection              |
| hmosite          | study site                 |
| htnmed           | hypertension medication    |
| hyperglycemia    | hyperglycemia diagnosis code |
| hyperlipidemia   | dyslipidemia               |
| hypertension     | hypertension               |
| hypoglycemia     | hypoglycemia diagnosis code |
| index.year       | index year                 |
| insulin.rxmd.analogpct | % AI dispensings in last year for index insulin prescriber |
| insulin.rxmd.spec | prescribing provider specialty for insulin dispensed at index |
| insulin.rxmd.type | index insulin provider type (NP/PA versus MD/PO ) |
| insulin.rxmd.yrs | years since prescribing provider of index insulin graduated |
| ip.count         | number of inpatient encounters |
| ldl              | low-denisty lipoprotein cholesterol |
| lipidmed         | cholesterol medication     |
| mavalvedisorder  | mitral or aortic valve heart disease |
| met              | metformin glucose lowering medication |
| mi.event         | myocardial infarction      |
| neurodisorder    | neuromuscular disorder     |
| nitrate          | nitrate medication         |
| platemed         | platelet inhibitor medication |
| ptvalvedisorder  | pulmonic or tricuspid valve heart disease |
| pvd              | peripheral vascular disease |
| racegrp          | race group                 |
| retinopathy      | retinopathy                |
| schizophrenia    | schizophrenia              |
| slgt2            | SGLT2 inhibitor class of glucose lowering medication |
| smoking.status   | smoking status             |
| stent            | stent placed in coronary artery |
| stroke.event     | stroke event               |
| sul              | sulfonyleurea glucose lowering medication |
| systolic         | systolic blood pressure    |
| tzd              | TZD glucose lowering medication |
| years.since.dm   | duration of diabetes in years |
Table 4: Part I of II - List of covariates considered in the various analyses and whether they are assumed to impact exposure decisions, censoring events, or outcomes.

| Covariate          | AMI | CHF | CVA | CVD | Death $\mu_{10}(t)$ | Initial insulin $\mu_{1}(0)$ | Insurance coverage $\mu_{3}(t)$ | Adherence to initial insulin $\mu_{j}(t)$ for $j = 5, 6, 8, 9$ | Time-dependent |
|--------------------|-----|-----|-----|-----|---------------------|-------------------------------|-------------------------------|---------------------------------------------------------------|----------------|
| afib               | 1   | 1   | 1   | 1   | 1                   | 0                             | 0                             | 0                                                             | 1              |
| age.at.index       | 1   | 1   | 1   | 1   | 1                   | 1                             | 1                             | 1                                                             | 0              |
| alcoholabuse       | 1   | 1   | 1   | 1   | 1                   | 1                             | 1                             | 1                                                             | 1              |
| anemia             | 1   | 1   | 1   | 1   | 0                   | 0                             | 0                             | 1                                                             | 1              |
| anticoag           | 1   | 1   | 1   | 1   | 0                   | 0                             | 0                             | 1                                                             | 1              |
| anxiety            | 1   | 1   | 1   | 1   | 0                   | 0                             | 0                             | 1                                                             | 1              |
| asthma             | 1   | 1   | 1   | 1   | 0                   | 0                             | 0                             | 1                                                             | 1              |
| bariatric          | 1   | 0   | 1   | 0   | 0                   | 0                             | 0                             | 1                                                             | 1              |
| bipolar            | 1   | 1   | 1   | 1   | 1                   | 1                             | 1                             | 1                                                             | 1              |
| bmi                | 1   | 1   | 1   | 1   | 0                   | 0                             | 0                             | 1                                                             | 1              |
| cagb               | 1   | 1   | 1   | 1   | 0                   | 1                             | 1                             | 1                                                             | 1              |
| cad                | 1   | 1   | 1   | 1   | 0                   | 1                             | 1                             | 1                                                             | 1              |
| cancer             | 0   | 0   | 0   | 0   | 0                   | 0                             | 0                             | 1                                                             | 1              |
| census.hsgrad      | 1   | 1   | 1   | 1   | 1                   | 0                             | 1                             | 1                                                             | 0              |
| census.medhhincome | 1   | 1   | 1   | 1   | 1                   | 0                             | 1                             | 1                                                             | 0              |
| cved               | 1   | 1   | 1   | 1   | 1                   | 0                             | 1                             | 1                                                             | 1              |
| chf                | 1   | 1   | 1   | 1   | 1                   | 0                             | 1                             | 1                                                             | 1              |
| chf.event          | 1   | 1   | 1   | 1   | 1                   | 0                             | 1                             | 1                                                             | 1              |
| ckd                | 1   | 1   | 1   | 1   | 1                   | 0                             | 1                             | 1                                                             | 1              |
| composite.protein  | 1   | 1   | 1   | 1   | 1                   | 0                             | 0                             | 1                                                             | 1              |
| connective         | 1   | 1   | 1   | 1   | 1                   | 0                             | 1                             | 1                                                             | 1              |
| copd               | 1   | 1   | 1   | 1   | 1                   | 0                             | 1                             | 1                                                             | 1              |
| dementia           | 1   | 1   | 1   | 1   | 1                   | 1                             | 1                             | 1                                                             | 1              |
| depression         | 1   | 1   | 1   | 1   | 1                   | 0                             | 1                             | 1                                                             | 1              |
| diastolic          | 1   | 1   | 1   | 0   | 0                   | 0                             | 0                             | 1                                                             | 1              |
| dpp4               | 1   | 1   | 1   | 1   | 1                   | 0                             | 1                             | 1                                                             | 1              |
| drugabuse.alt      | 1   | 1   | 1   | 1   | 1                   | 0                             | 1                             | 1                                                             | 1              |
| drugcount          | 0   | 0   | 0   | 0   | 0                   | 0                             | 0                             | 1                                                             | 0              |
| early.adopter      | 0   | 0   | 0   | 0   | 0                   | 1                             | 0                             | 1                                                             | 0              |
| elixhauser         | 0   | 0   | 0   | 0   | 0                   | 0                             | 0                             | 1                                                             | 0              |
| flag.incident      | 1   | 1   | 1   | 1   | 1                   | 0                             | 0                             | 1                                                             | 0              |
| gender             | 1   | 1   | 1   | 1   | 1                   | 0                             | 0                             | 1                                                             | 0              |
| gfr                | 1   | 1   | 1   | 1   | 1                   | 0                             | 0                             | 1                                                             | 1              |
| glp1               | 1   | 1   | 1   | 1   | 1                   | 0                             | 0                             | 1                                                             | 1              |
| hdl                | 1   | 0   | 1   | 1   | 1                   | 0                             | 0                             | 1                                                             | 1              |
| hgba1c             | 1   | 1   | 1   | 1   | 1                   | 1                             | 0                             | 1                                                             | 1              |

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### Table 5: Part II of II - List of covariates considered in the various analyses and whether they are assumed to impact exposure decisions, censoring events, or outcomes.

| Covariate          | AMI | CHF | CVA | CVD | Death $\mu_{10}(t)$ | Initial insulin $\mu_{1}(0)$ | Insurance coverage $\mu_{3}(t)$ | Adherence to initial insulin $\mu_{j}(t)$ for $j = 5, 6, 8, 9$ | Time-dependent |
|--------------------|-----|-----|-----|-----|----------------------|-------------------------------|-------------------------------|-------------------------------------------------|----------------|
| hiv                | 1   | 1   | 1   | 1   | 1                    | 0                             | 1                             | 0                                               | 1              |
| hmosite            | 0   | 0   | 0   | 0   | 0                    | 1                             | 1                             | 0                                               | 0              |
| htnmed             | 1   | 1   | 1   | 0   | 0                    | 0                             | 0                             | 0                                               | 1              |
| hyperglycemia      | 1   | 1   | 1   | 1   | 1                    | 0                             | 0                             | 1                                               | 1              |
| hyperlipidemia     | 1   | 1   | 1   | 1   | 1                    | 0                             | 0                             | 0                                               | 1              |
| hypertension       | 1   | 1   | 1   | 1   | 1                    | 0                             | 0                             | 1                                               | 1              |
| hypoglycemia       | 1   | 1   | 1   | 1   | 1                    | 1                             | 0                             | 1                                               | 1              |
| index.year         | 0   | 0   | 0   | 0   | 0                    | 1                             | 0                             | 0                                               | 0              |
| insulin.rxmd.analogpct | 0   | 0   | 0   | 0   | 0                    | 1                             | 0                             | 0                                               | 0              |
| insulin.rxmd.spec  | 0   | 0   | 0   | 0   | 0                    | 1                             | 0                             | 0                                               | 0              |
| insulin.rxmd.type  | 0   | 0   | 0   | 0   | 0                    | 1                             | 0                             | 0                                               | 0              |
| insulin.rxmd.yrs   | 0   | 0   | 0   | 0   | 0                    | 1                             | 0                             | 0                                               | 0              |
| ip.count           | 1   | 1   | 1   | 1   | 1                    | 0                             | 1                             | 0                                               | 1              |
| ldl                | 1   | 0   | 1   | 1   | 0                    | 0                             | 0                             | 0                                               | 1              |
| lipidmed           | 1   | 0   | 1   | 1   | 0                    | 0                             | 0                             | 0                                               | 1              |
| mavalvedisorder    | 0   | 1   | 1   | 1   | 1                    | 0                             | 0                             | 0                                               | 1              |
| met                | 1   | 1   | 1   | 1   | 1                    | 0                             | 0                             | 0                                               | 1              |
| mi.event           | 1   | 1   | 1   | 1   | 1                    | 0                             | 1                             | 0                                               | 1              |
| neurodisorder      | 0   | 0   | 0   | 0   | 0                    | 0                             | 1                             | 0                                               | 1              |
| nitrate            | 1   | 1   | 1   | 1   | 1                    | 0                             | 0                             | 0                                               | 1              |
| platemed           | 1   | 1   | 1   | 1   | 1                    | 0                             | 0                             | 0                                               | 1              |
| ptvalvedisorder    | 0   | 1   | 0   | 1   | 1                    | 0                             | 0                             | 0                                               | 1              |
| pvd                | 1   | 1   | 1   | 1   | 1                    | 0                             | 1                             | 0                                               | 1              |
| racegrp            | 1   | 1   | 1   | 1   | 1                    | 0                             | 1                             | 1                                               | 0              |
| retinopathy        | 1   | 1   | 1   | 1   | 1                    | 0                             | 0                             | 0                                               | 1              |
| schizophrenia      | 1   | 1   | 1   | 1   | 1                    | 0                             | 1                             | 1                                               | 1              |
| sglt2              | 1   | 1   | 1   | 1   | 1                    | 0                             | 1                             | 1                                               | 1              |
| smoking.status     | 1   | 1   | 1   | 1   | 1                    | 0                             | 0                             | 1                                               | 0              |
| stent              | 1   | 1   | 1   | 1   | 1                    | 0                             | 1                             | 1                                               | 1              |
| stroke.event       | 1   | 1   | 1   | 1   | 1                    | 0                             | 1                             | 1                                               | 1              |
| sul                | 1   | 1   | 1   | 1   | 1                    | 1                             | 0                             | 0                                               | 1              |
| systolic           | 1   | 1   | 1   | 1   | 1                    | 0                             | 0                             | 0                                               | 1              |
| tzd                | 1   | 1   | 1   | 1   | 1                    | 1                             | 0                             | 0                                               | 1              |
| years.since.dm     | 1   | 1   | 1   | 1   | 1                    | 0                             | 0                             | 0                                               | 0              |

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## Table 6: Cutoffs used to discretize continuous covariates.

| Variable             | Cutoffs                           |
|----------------------|-----------------------------------|
| age.at.index (years) | 35; 45; 55; 65; 75                |
| bmi (Kg/m²)          | 18.5; 25; 30; 35; 40              |
| census.hsgrad        | 0.5                               |
| census.medhhincome   | 30000; 50000; 70000; 90000         |
| diastolic (mm Hg)    | 80; 90; 100                        |
| drugcount            | 2; 3; 4; 5; 6; 7; 8; 9             |
| elixhauser score     | 1; 3; 5                            |
| gfr (mL/1.73 m²/min) | 15; 30; 45; 60; 90                 |
| hdl (mg/dL)          | 40; 50; 60                         |
| hgba1c (%)           | 7; 7.5; 8; 8.5; 9; 10              |
| insulin.rxmd.analogpct| 0.1; 0.5; 0.9                      |
| insulin.rxmd.yrs     | 5; 20                              |
| ip.count             | 1; 2                               |
| ldl (mg/dL)          | 70; 100; 130                       |
| systolic (mm Hg)     | 120; 140; 160                      |
| t                    | 1; 2; 3; 4; 6; 8; 10; 12; 16        |
| years.since.dm      | 1; 6; 10                            |
Table 7: PS estimation approach 1 in AMI primary analysis: Logistic model for the probability of right-censoring due to a switch from analog-containing to human-only insulin therapy. Model fitted with 126617 observations from 18318 unique patients. Reference categories: $t < 1$, $55 \leq \text{age.at.index} < 65$, genderM, racegrp6:WHITE, smoking.statusNEVER/UNK, hgba1c $< 7$, $50000 \leq \text{census.medhhincome} < 70000$, census.hsgrad $\geq 0.5$. Indicators of missing covariate measurement are denoted by $I.$ (e.g., $I.$hgba1c denotes the absence of hgba1c monitoring at quarter 't').

| Covariate                  | Coef | OR  |
|----------------------------|------|-----|
| (Intercept)                | -3.781|     |
| $t$ in $[1;2]$             | -0.156| 0.855|
| $t$ in $[2;3]$             | 0.377 | 1.457|
| $t$ in $[3;4]$             | 0.039 | 1.039|
| $t$ in $[4;6]$             | 2e-03 | 1.002|
| $t$ in $[6;8]$             | 4e-03 | 1.004|
| $t$ in $[8;10]$            | 0.107 | 1.113|
| $t$ in $[10;12]$           | 0.089 | 1.093|
| $t$ in $[12;16]$           | 0.265 | 1.304|
| $t \geq 16$               | 0.303 | 1.354|
| age.at.index < 35          | -0.101| 0.904|
| age.at.index in $[35;45]$  | 1e-03 | 1.001|
| age.at.index in $[45;55]$  | -0.036| 0.964|
| age.at.index in $[65;75]$  | 0.094 | 1.098|
| age.at.index $\geq 75$    | 0.141 | 1.152|
| genderF                   | 0.096 | 1.101|
| racegrp1:HISPANIC         | 0.188 | 1.206|
| racegrp2:BLACK            | -0.016| 0.984|
| racegrp3:HI/PI            | 0.38  | 1.462|
| racegrp4:ASIAN            | 0.127 | 1.136|
| racegrp5:NATIV            | -0.115| 0.892|
| racegrp7:MISS             | -0.044| 0.957|
| smoking.statusCURRENT    | -6e-02| 0.942|
| smoking.statusPAST        | 0.049 | 1.051|
| cabg                      | -0.089| 0.914|
| cad                       | 2e-03 | 1.002|
| cevd                      | 0.106 | 1.112|

| Covariate                  | Coef | OR  |
|----------------------------|------|-----|
| chf                        | 0.068 | 1.07 |
| stent                      | -0.135| 0.874|
| chf.event                  | 0.303 | 1.354|
| hgba1c in $[7;7.5]$        | -0.103| 0.902|
| hgba1c in $[7.5;8]$        | 0.318 | 1.374|
| hgba1c in $[8;8.5]$        | 0.696 | 2.005|
| hgba1c in $[8.5;9]$        | 0.754 | 2.126|
| hgba1c in $[9;10]$         | 0.955 | 2.599|
| hgba1c $\geq 10$          | 1.006 | 2.735|
| stroke.event               | 0.429 | 1.535|
| l.hgba1c                   | -1.414| 0.243|
| alcoholabuse               | 0.098 | 1.103|
| bipolar                    | 0.113 | 1.12 |
| depression                 | 0.087 | 1.09 |
| drugabuse.alt              | 0.315 | 1.37 |
| schizophrenia              | 0.139 | 1.149|
| census.medhhincome <30000  | 0.114 | 1.12 |
| census.medhhincome in $[30000;50000]$ | 0.068 | 1.07 |
| census.medhhincome in $[70000;90000]$ | 0.043 | 1.039|
| census.medhhincome $\geq 90000$ | 0.057 | 1.059|
| anxiety                    | 0.033 | 1.034|
| dementia                   | 0.193 | 1.213|
| hyperglycemia              | 0.272 | 1.313|
| hypoglycemia               | 0.779 | 2.179|
| I.census.medhhincome       | -10.214 | 1 |
| I.census.hsgrad            | 9.496 | 13300.155|

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Table 8: PS estimation approach 2 in AMI primary analysis (Part I of II): Logistic model for the probability of right-censoring due to a switch from analog-containing to human-only insulin therapy. Model fitted with 126617 observations from 18318 unique patients. Reference categories: 55 \leq \text{age.at.index} < 65, \text{ip.count} < 1, 60 \leq \text{gfr} < 90, \text{hdl} < 40, \text{hgba1c} < 7, 70 \leq \text{ldl} < 100, 120 \leq \text{systolic} < 140, 6 \leq \text{years.since.dm} < 10, \text{diastolic} < 80, 50000 \leq \text{census.medhhincome} < 70000, \text{census.hsgrad} \geq 0.5, 30 \leq \text{bmi} < 35, \text{t} < 1, \text{genderM}, \text{racegrp6:WHITE}, \text{smoking.statusNEVER/UNK}, \text{flag.incidentUnknown}, \text{composite.protein1:NORML}. Indicators of missing covariate measurement are denoted by I.* (e.g., I.hgba1c denotes the absence of hgba1c monitoring at quarter 't').

| Covariate                  | Coef | OR  |
|----------------------------|------|-----|
| (Intercept)                | -4.371 |     |
| age.at.index <35           | 0.099 | 1.104 |
| age.at.index in [35;45[    | 0.094 | 1.099 |
| age.at.index in [45;55[    | 0.017 | 1.017 |
| age.at.index in [65;75[    | 2e-03 | 1.002 |
| age.at.index \geq 75       | 3e-03 | 1.003 |
| genderF                    | 0.074 | 1.077 |
| racegrp1:HISPANIC          | 0.159 | 1.172 |
| racegrp2:BLACK             | -0.033 | 0.968 |
| racegrp3:HI/PI             | 0.342 | 1.408 |
| racegrp4:ASIAN             | 0.1   | 1.105 |
| racegrp5:NATIV             | -0.082 | 0.922 |
| smoking.statusCURRENT      | -0.087 | 0.917 |
| smoking.statusPAST         | 0.018 | 1.019 |
| mi.event                   | 0.17  | 1.185 |
| bariatric                  | -1.079 | 0.34  |
| cabg                       | -0.262 | 0.769 |
| cad                        | -0.108 | 0.897 |
| cevd                       | -0.061 | 0.941 |
| chf                        | -0.104 | 0.901 |
| hyperlipidemia             | 0.102 | 1.107 |
| hypertension               | 0.071 | 1.073 |
| pvd                        | -0.150 | 0.861 |
| stent                      | -0.291 | 0.748 |
| chf.event                  | 0.112 | 1.118 |
| htnmed                     | 0.191 | 1.211 |
| ip.count in [1;2[           | 0.24  | 1.272 |
| ip.count \geq 2            | 0.458 | 1.581 |

| Covariate                  | Coef | OR  |
|----------------------------|------|-----|
| lipidmed                   | 0.125 | 1.133 |
| nitrate                    | 0.062 | 1.064 |
| platemed                   | -0.021 | 0.979 |
| gfr <15                    | -0.281 | 0.755 |
| gfr in [15;30[             | 0.025 | 1.025 |
| gfr in [30;45[             | 9e-02 | 1.094 |
| gfr in [45;60[             | 5e-02 | 1.051 |
| gfr \geq 90               | 0.036 | 1.037 |
| hd1 in [40;50[             | -0.061 | 0.941 |
| hd1 in [50;60[             | -0.032 | 0.969 |
| hd1 \geq 60               | -0.053 | 0.948 |
| hd1a in [7;7.5[            | -4e-02 | 0.961 |
| hd1a in [7.5;8[            | 0.402 | 1.494 |
| hd1a in [8;8.5[            | 0.789 | 2.2  |
| hd1a in [8.5;9[            | 0.853 | 2.348 |
| hd1a in [9;10[             | 1.057 | 2.878 |
| hd1a \geq 10              | 1.14  | 3.127 |
| ldl <70                   | -0.022 | 0.978 |
| ldl in [100;130[          | -0.071 | 0.931 |
| ldl \geq 130              | -0.042 | 0.959 |
| stroke.event              | 0.418 | 1.519 |
| systolic <120             | -0.062 | 0.939 |
| systolic in [140;160]      | -0.124 | 0.884 |
| systolic \geq 160         | -0.112 | 0.894 |
| I.gfr                     | -0.121 | 0.886 |
| I.hdl                     | -0.179 | 0.836 |
| I.hgba1c                  | -0.814 | 0.443 |
| I.ldl                     | -0.018 | 0.982 |
| I.systolic                | -0.4   | 0.67  |
Table 9: PS estimation approach 2 in AMI primary analysis (Part II of II): Logistic model for the probability of right-censoring due to a switch from analog-containing to human-only insulin therapy. Model fitted with 126617 observations from 18318 unique patients. Reference categories: 55 ≤ age.at.index < 65, ip.count < 1, 60 ≤ gfr < 90, hgba1c < 7, 70 ≤ ldl < 100, 120 ≤ systolic < 140, 6 ≤ years.since.dm < 10, diastolic < 80, 50000 ≤ census.medhhincome < 70000, census.hsgrad ≥ 0.5, 30 ≤ bmi < 35, t < 1, genderM, racegrp6:WHITE, smoking.statusNEVER/UNK, flag.incidentUnknown, composite.protein1:NORML. Indicators of missing covariate measurement are denoted by I.* (e.g., I.hgba1c denotes the absence of hgba1c monitoring at quarter ‘t’).

| Covariate                  | Coef  | OR   |
|----------------------------|-------|------|
| years.since.dm < 1         | 0.048 | 1.049|
| years.since.dm in [1;6[    | -0.106| 0.9  |
| years.since.dm ≥ 10        | 0.188 | 1.207|
| flag.incidentNo            | 0.263 | 1.3  |
| flag.incidentYes           | 0.193 | 1.213|
| alcoholabuse               | -5e-03| 0.995|
| bipolar                    | 0.059 | 1.061|
| connective                 | -0.047| 0.954|
| depression                 | 1e-03 | 1.001|
| drugabuse.alt              | 0.219 | 1.245|
| hiv                        | -0.314| 0.73 |
| retinopathy                | 8e-03 | 1.008|
| schizophrenia              | 0.059 | 1.061|
| diastolic in [80;90[       | -0.018| 0.982|
| diastolic in [90;100[      | -0.159| 0.853|
| diastolic ≥ 100            | -0.177| 0.837|
| l.diastolic                | 0.028 | 1.029|
| census.medhhincome < 30000 | 0.111 | 1.118|
| census.medhhincome in [30000;50000[ | 0.065 | 1.067|
| census.medhhincome in [70000;90000[ | 0.043 | 1.044|
| census.medhhincome ≥ 90000 | 0.045 | 1.046|
| census.hsgrad < 0.5       | 0.057 | 1.058|
| afib                       | -0.043| 0.958|
| anxiety                    | -0.045| 0.956|
| asthma                     | 0.047 | 1.048|
| ckd                        | 0.175 | 1.191|
| copd                       | 0.254 | 1.289|
| dementia                   | 0.194 | 1.214|
| anemia                     | 0.184 | 1.202|
| dpp4                       | -0.524| 0.592|
| glp1                       | -0.565| 0.568|
| met                        | 3e-02 | 1.031|
| anticoag                   | 0.095 | 1.099|
| sul                        | 0.146 | 1.157|
| tzd                        | -0.111| 0.895|
| bmi < 18.5                 | 0.208 | 1.232|
| bmi in [18.5;25[          | -0.072| 0.93 |
| bmi in [25;30[            | -0.023| 0.977|
| bmi in [35;40[            | -4e-03| 0.996|
| bmi ≥ 40                   | 0.038 | 1.039|
| composite.protein0:UNK     | -0.131| 0.877|
| composite.protein2:MICRO   | 6e-03 | 1.006|
| composite.protein3:MACRO   | -0.104| 0.901|
| hyperglycemia              | 0.172 | 1.188|
| hypoglycemia               | 0.665 | 1.944|
| l.census.medhhincome       | -10.209| 0   |
| l.census.hsgrad            | 9.671 | 15855.835|
| l.bmi                      | -0.379| 0.685|
| l.composite.protein        | -0.331| 0.718|
| t in [1;2[                | 0.045 | 1.046|
| t in [2;3[                | 0.662 | 1.939|
| t in [3;4[                | 0.312 | 1.366|
| t in [4;6[                | 0.25  | 1.283|
| t in [6;8[                | 0.242 | 1.273|
| t in [8;10[               | 0.334 | 1.397|
| t in [10;12[              | 0.325 | 1.384|
| t in [12;16[              | 0.51  | 1.665|
| t ≥ 16                    | 0.556 | 1.744|

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Table 10: PS estimation approach 3 in AMI primary analysis (Part I of II): Logistic model for the probability of right-censoring due to a switch from analog-containing to human-only insulin therapy. Model fitted with 126617 observations from 18318 unique patients. Reference categories: $55 \leq \text{age.at.index} < 65$, genderM, racegrp6:WHITE, $50000 \leq \text{census.medhhincome} < 70000$, census.hsgrad $\geq 0.5$, smoking.statusNEVER/UNK, elixhauser $\geq 5$, drugcount$\geq 9$, hgba1c $< 7$, ip.count $< 1$, $60 \leq \text{gfr} < 90$, hdl $< 40$, $70 \leq \text{ldl} < 100$, $120 \leq \text{systolic} < 140$, $6 \leq \text{years.since.dm} < 10$, flag.incidentUnknown, diastolic $< 80$, $30 \leq \text{bmi} < 35$, composite.protein1: NORML, $t < 1$. Indicators of missing covariate measurement are denoted by I.* (e.g., I.hgba1c denotes the absence of hgba1c monitoring at quarter ‘t’).

| Covariate | Coef | OR  |
|-----------|------|-----|
| (Intercept) | -4.508 | 1.089 |
| age.at.index $< 35$ | 0.085 | 1.089 |
| age.at.index in $[35;45[$ | 0.091 | 1.095 |
| age.at.index in $[45;55[$ | 0.017 | 1.017 |
| age.at.index in $[65;75[$ | 7e-03 | 1.007 |
| age.at.index $\geq 75$ | 7e-03 | 1.007 |
| genderF | 0.079 | 1.082 |
| racegrp1:HISPANIC | 0.155 | 1.168 |
| racegrp2:BLACK | -0.032 | 0.969 |
| racegrp3:HI/PI | 0.341 | 1.406 |
| racegrp4:ASIAN | 0.101 | 1.106 |
| racegrp5:NATIV | -0.078 | 0.925 |
| racegrp7:MISS | 9e-02 | 1.094 |
| census.medhhincome $< 30000$ | 0.11 | 1.116 |
| census.medhhincome in $[30000;50000[$ | 0.062 | 1.064 |
| census.medhhincome in $[70000;90000[$ | 0.043 | 1.043 |
| census.medhhincome $\geq 90000$ | 0.047 | 1.048 |
| census.hsgrad $< 0.5$ | 5e-02 | 1.052 |
| smoking.statusCURRENT | -0.088 | 0.915 |
| smoking.statusPAST | 0.021 | 1.021 |
| elixhauser in $[1;3[$ | -0.053 | 0.948 |
| elixhauser in $[3;5[$ | 2e-02 | 1.02 |
| drugcount $< 2$ | 0.212 | 1.237 |
| drugcount in $[2;3[$ | 0.17 | 1.185 |
| drugcount in $[3;4[$ | 0.214 | 1.239 |
| drugcount in $[4;5[$ | 0.071 | 1.074 |
| drugcount in $[5;6[$ | 0.062 | 1.064 |
| drugcount in $[6;7[$ | 0.051 | 1.052 |
| drugcount in $[7;8[$ | 0.036 | 1.036 |
| drugcount in $[8;9[$ | 0.066 | 1.069 |
| alcoholabuse | -5e-03 | 0.995 |
| anxiety | -0.038 | 0.963 |

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Table 11: PS estimation approach 3 in AMI primary analysis (Part II of II): Logistic model for the probability of right-censoring due to a switch from analog-containing to human-only insulin therapy. Model fitted with 126617 observations from 18318 unique patients. Reference categories: 55≤age.at.index<65, genderM, racegrp6:WHITE, 50000≤census.medhhincome<70000, census.hsgad≥0.5, smoking.statusNEVER/UNK, elixhauser≥5, drugcounteq9, hgba1c<7, ip.count<1, 60≤gfr<90, hdl<40, 70≤ldl<100, 120≤systolic<140, 6≤years.since.dm<10, flag.incidentUn-known, diastolic<80, 30≤bmi<35, composite.protein1:NORML, t<1. Indicators of missing covariate measurement are denoted by I.* (e.g., I.hgba1c denotes the absence of hgba1c monitoring at quarter ‘t’).

| Covariate               | Coef | OR  |
|-------------------------|------|-----|
| nitrate                 | 0.071| 1.074|
| platemed               | -0.014| 0.986|
| gfr <15                | -0.28 | 0.756|
| gfr in [15;30[        | 0.037 | 1.037|
| gfr in [30;45[       | 0.1   | 1.105|
| gfr in [45;60[       | 0.055 | 1.057|
| gfr ≥90               | 0.031 | 1.031|
| hdl in [40;50[       | -0.062| 0.94 |
| hdl in [50;60[       | -0.033| 0.967|
| hdl ≥60               | -0.055| 0.946|
| ldl <70               | -2e-02| 0.981|
| ldl in [100;130[     | -0.074| 0.928|
| ldl ≥130              | -0.049| 0.953|
| systolic <120         | -0.062| 0.94 |
| systolic in [140;160[| -0.122| 0.885|
| systolic ≥160         | -0.108| 0.898|
| I.gfr                 | -0.122| 0.885|
| I.hdl                 | -0.178| 0.837|
| I.ldl                 | -0.019| 0.981|
| I.systolic            | -0.379| 0.685|
| years.since.dm <1     | 0.044 | 1.045|
| years.since.dm in [1;6[| -0.107| 0.899|
| years.since.dm ≥10    | 0.188 | 1.207|
| flag.incidentNo       | 0.261 | 1.298|
| flag.incidentYes      | 0.196 | 1.217|
| connective            | -4e-02| 0.961|
| hiv                   | -0.318| 0.727|
| retinopathy           | 5e-03 | 1.006|
| diastolic in [80;90[  | -0.019| 0.981|
| diastolic in [90;100[ | -0.16  | 0.852|
| diastolic ≥100        | -0.179| 0.836|
| I.diastolic           | 9e-03 | 1.009|

| Covariate               | Coef | OR  |
|-------------------------|------|-----|
| afib                   | -0.035| 0.966|
| asthma                 | 0.054 | 1.055|
| ckd                    | 0.174 | 1.19 |
| copd                   | 0.265 | 1.303|
| anemia                 | 0.19  | 1.21 |
| dpp4                   | -0.508| 0.602|
| glp1                   | -0.557| 0.573|
| met                    | 0.049 | 1.05 |
| anticoag               | 0.101 | 1.107|
| slgt2                  | -9.909| 0    |
| sul                    | 0.168 | 1.182|
| tzd                    | -0.093| 0.911|
| bmi <18.5              | 0.205 | 1.227|
| bmi in [18.5;25[      | -7e-02| 0.932|
| bmi in [25;30[        | -0.022| 0.979|
| bmi in [35;40[        | -1e-03| 0.999|
| bmi ≥40               | 4e-02 | 1.041|
| composite.protein0:UNK | -0.122| 0.885|
| composite.protein2:MICRO| 7e-03 | 1.007|
| composite.protein3:MACRO| -0.101| 0.904|
| I.bmi                 | -0.378| 0.685|
| I.composite.protein    | -0.331| 0.718|
| t in [1;2[            | 0.037 | 1.038|
| t in [2;3[            | 0.656 | 1.927|
| t in [3;4[            | 0.307 | 1.36 |
| t in [4;6[            | 0.245 | 1.277|
| t in [6;8[            | 0.237 | 1.268|
| t in [8;10[           | 0.329 | 1.39 |
| t in [10;12[          | 0.32  | 1.378|
| t in [12;16[          | 0.505 | 1.657|
| t ≥16                 | 0.552 | 1.736|

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eTable 12: PS estimation approach 4 in AMI primary analysis: Super learner estimator for the probability of right-censoring due to a switch from analog-containing to human-only insulin therapy. Estimator derived based on 126617 observations from 18318 unique patients. Three learners were considered corresponding with three logistic models described in eTables 7-11. The weighted average (SL weights) of the 3 learners that define the super learner was constructed based on 10-fold cross-validation (CV).

|                | Logistic model 1 (eTable 7) | Logistic model 2 (eTables 8-9) | Logistic model 3 (eTables 10-11) |
|----------------|-----------------------------|-------------------------------|---------------------------------|
| CV risk        | 0.03492                     | 0.0346                        | 0.0346                          |
| SL weights     | 0.05641                     | 0.61874                       | 0.32485                         |
**eTable 13: Distribution of type of initial insulin therapy for patients in the main cohort by site and year of cohort entry.**

| Year | Site 1  | Site 2  | Site 3  | Site 4  |
|------|---------|---------|---------|---------|
|      | Analog % | Human % | Analog % | Human % | Analog % | Human % | Analog % | Human % |
| 2005 | 11.01    | 88.99   | 9.2     | 90.8    | 1.26     | 98.74   | 88.37    | 11.63   |
| 2006 | 20.55    | 79.45   | 11.94   | 88.06   | 2.67     | 97.33   | 94.07    | 5.93    |
| 2007 | 29.57    | 70.43   | 9.99    | 90.01   | 4.16     | 95.84   | 92.48    | 7.52    |
| 2008 | 34.71    | 65.29   | 11.49   | 88.51   | 7.13     | 92.87   | 95.08    | 4.92    |
| 2009 | 29.3     | 70.7    | 11.51   | 88.49   | 5.29     | 94.71   | 97.36    | 2.64    |
| 2010 | 14.76    | 85.24   | 7.86    | 92.14   | 2.59     | 97.41   | 96.55    | 3.45    |
| 2011 | 8.92     | 91.08   | 7.95    | 92.05   | 3.92     | 96.08   | 98.34    | 1.66    |
| 2012 | 5.29     | 94.71   | 8.52    | 91.48   | 3.35     | 96.65   | 97.77    | 2.23    |
| 2013 | 3.99     | 96.01   | 8.9     | 91.1    | 3.68     | 96.32   | 97.92    | 2.08    |

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eTable 14: Distribution of follow-up time (expressed in 90-day intervals) for patients continuously exposed to analog-containing insulin therapy in the primary AMI analyses (all sites combined).

| Follow-up time | Frequency | %    | Cumulative Frequency | Cumulative % |
|----------------|-----------|------|----------------------|--------------|
| [1, 2]         | 1955      | 10.33| 1955                 | 10.33        |
| [2, 3]         | 1211      | 6.40 | 3166                 | 16.73        |
| [3, 4]         | 5848      | 30.90| 9014                 | 47.62        |
| [4, 5]         | 1675      | 8.85 | 10689                | 56.47        |
| [5, 6]         | 1004      | 5.30 | 11693                | 61.78        |
| [6, 7]         | 857       | 4.53 | 12550                | 66.30        |
| [7, 8]         | 761       | 4.02 | 13311                | 70.32        |
| [8, 9]         | 608       | 3.21 | 13919                | 73.54        |
| [9, 10]        | 518       | 2.74 | 14437                | 76.27        |
| [10, 11]       | 464       | 2.45 | 14901                | 78.72        |
| [11, 12]       | 392       | 2.07 | 15293                | 80.80        |
| [12, 13]       | 370       | 1.95 | 15663                | 82.75        |
| [13, 17]       | 1143      | 6.04 | 16806                | 88.79        |
| [17, 21]       | 879       | 4.64 | 17685                | 93.43        |
| [21, 25]       | 621       | 3.28 | 18306                | 96.71        |
| [25, 29]       | 350       | 1.85 | 18656                | 98.56        |
| [29, 33]       | 192       | 1.01 | 18848                | 99.58        |
| [33, 37]       | 71        | 0.38 | 18919                | 99.95        |
| ≥ 37           | 9         | 0.05 | 18928                | 100.00       |
| Missing        | 0         | 0.00 | 18928                | 100.00       |
**eTable 15**: Distribution of follow-up time (expressed in 90-day intervals) for patients continuously exposed to human-only insulin therapy in the primary AMI analyses (all sites combined).

| Follow-up time | Frequency | %   | Cumulative Frequency | Cumulative % |
|----------------|-----------|-----|----------------------|--------------|
| [1, 2]         | 8951      | 8.24| 8951                 | 8.24         |
| [2, 3]         | 7098      | 6.53| 16049                | 14.77        |
| [3, 4]         | 34325     | 31.59| 50374                | 46.35        |
| [4, 5]         | 10653     | 9.80| 61027                | 56.16        |
| [5, 6]         | 6156      | 5.66| 67183                | 61.82        |
| [6, 7]         | 5322      | 4.90| 72505                | 66.72        |
| [7, 8]         | 4523      | 4.16| 77028                | 70.88        |
| [8, 9]         | 3848      | 3.54| 80876                | 74.42        |
| [9, 10]        | 3044      | 2.80| 83920                | 77.22        |
| [10, 11]       | 2711      | 2.49| 86631                | 79.72        |
| [11, 12]       | 2412      | 2.22| 89043                | 81.94        |
| [12, 13]       | 2161      | 1.99| 91204                | 83.93        |
| [13, 17]       | 5977      | 5.50| 97181                | 89.43        |
| [17, 21]       | 4112      | 3.78| 101293               | 93.21        |
| [21, 25]       | 2888      | 2.66| 104181               | 95.87        |
| [25, 29]       | 2354      | 2.17| 106535               | 98.03        |
| [29, 33]       | 1270      | 1.17| 107805               | 99.20        |
| [33, 37]       | 768       | 0.71| 108573               | 99.91        |
| ≥ 37           | 99        | 0.09| 108672               | 100.00       |
| Missing        | 0         | 0.00| 108672               | 100.00       |

**eTable 16**: Summary statistics of the distribution of follow-up time (expressed in 90-day intervals) by exposure regimen in the primary AMI analyses (all sites combined).

| Exposure   | N     | Min. | 1st Qu. | Median | Mean  | 3rd Qu. | Max. |
|------------|-------|------|---------|--------|-------|---------|------|
| Analog     | 18928 | 1    | 3       | 4      | 6.95  | 9       | 37   |
| Human      | 108672| 1    | 3       | 4      | 6.98  | 9       | 37   |

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Table 17: Distribution of follow-up time (expressed in 90-day intervals) for patients continuously exposed to analog-containing insulin therapy in the primary CHF analyses (all sites combined).

| Follow-up time | Frequency | %    | Cumulative Frequency | Cumulative % |
|----------------|-----------|------|----------------------|--------------|
| [1, 2]         | 2023      | 10.69| 2023                 | 10.69        |
| [2, 3]         | 1243      | 6.57 | 3266                 | 17.25        |
| [3, 4]         | 5808      | 30.68| 9074                 | 47.94        |
| [4, 5]         | 1667      | 8.81 | 10741                | 56.75        |
| [5, 6]         | 1003      | 5.30 | 11744                | 62.05        |
| [6, 7]         | 859       | 4.54 | 12603                | 66.58        |
| [7, 8]         | 760       | 4.02 | 13363                | 70.60        |
| [8, 9]         | 605       | 3.20 | 13968                | 73.80        |
| [9, 10]        | 524       | 2.77 | 14492                | 76.56        |
| [10, 11]       | 447       | 2.36 | 14939                | 78.93        |
| [11, 12]       | 392       | 2.07 | 15331                | 81.00        |
| [12, 13]       | 369       | 1.95 | 15700                | 82.95        |
| [13, 17]       | 1135      | 6.00 | 16835                | 88.94        |
| [17, 21]       | 873       | 4.61 | 17708                | 93.55        |
| [21, 25]       | 605       | 3.20 | 18313                | 96.75        |
| [25, 29]       | 344       | 1.82 | 18657                | 98.57        |
| [29, 33]       | 193       | 1.02 | 18850                | 99.59        |
| [33, 37]       | 69        | 0.36 | 18919                | 99.95        |
| ≥ 37           | 9         | 0.05 | 18928                | 100.00       |
| Missing        | 0         | 0.00 | 18928                | 100.00       |
**eTable 18:** Distribution of follow-up time (expressed in 90-day intervals) for patients continuously exposed to human-only insulin therapy in the primary CHF analyses (all sites combined).

| Follow-up time | Frequency | %    | Cumulative Frequency | Cumulative % |
|----------------|-----------|------|----------------------|--------------|
| [1, 2]         | 9326      | 8.58 | 9326                 | 8.58         |
| [2, 3]         | 7219      | 6.64 | 16545                | 15.22        |
| [3, 4]         | 34131     | 31.41| 50676                | 46.63        |
| [4, 5]         | 10647     | 9.80 | 61323                | 56.43        |
| [5, 6]         | 6144      | 5.65 | 67467                | 62.08        |
| [6, 7]         | 5317      | 4.89 | 72784                | 66.98        |
| [7, 8]         | 4504      | 4.14 | 77288                | 71.12        |
| [8, 9]         | 3846      | 3.54 | 81134                | 74.66        |
| [9, 10]        | 3042      | 2.80 | 84176                | 77.46        |
| [10, 11]       | 2709      | 2.49 | 86885                | 79.95        |
| [11, 12]       | 2368      | 2.18 | 89253                | 82.13        |
| [12, 13]       | 2137      | 1.97 | 91390                | 84.10        |
| [13, 17]       | 5883      | 5.41 | 97273                | 89.51        |
| [17, 21]       | 4081      | 3.76 | 101354               | 93.27        |
| [21, 25]       | 2844      | 2.62 | 104198               | 95.88        |
| [25, 29]       | 2340      | 2.15 | 106538               | 98.04        |
| [29, 33]       | 1267      | 1.17 | 107805               | 99.20        |
| [33, 37]       | 768       | 0.71 | 108573               | 99.91        |
| ≥ 37           | 99        | 0.09 | 108672               | 100.00       |
| Missing        | 0         | 0.00 | 108672               | 100.00       |

**eTable 19:** Summary statistics of the distribution of follow-up time (expressed in 90-day intervals) by exposure regimen in the primary CHF analyses (all sites combined).

| Exposure | N     | Min. | 1st Qu. | Median | Mean  | 3rd Qu. | Max. |
|----------|-------|------|---------|--------|-------|---------|------|
| Analog   | 18928 | 1    | 3       | 4      | 6.90  | 9       | 37   |
| Human    | 108672| 1    | 3       | 4      | 6.94  | 9       | 37   |

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eTable 20: Distribution of follow-up time (expressed in 90-day intervals) for patients continuously exposed to analog-containing insulin therapy in the primary CVA analyses (all sites combined).

| Follow-up time | Frequency | %   | Cumulative Frequency | Cumulative % |
|----------------|-----------|-----|----------------------|--------------|
| [1, 2[         | 1937      | 10.23 | 1937                 | 10.23        |
| [2, 3[         | 1223      | 6.46  | 3160                 | 16.69        |
| [3, 4[         | 5842      | 30.86 | 9002                 | 47.56        |
| [4, 5[         | 1682      | 8.89  | 10684                | 56.45        |
| [5, 6[         | 1004      | 5.30  | 11688                | 61.75        |
| [6, 7[         | 853       | 4.51  | 12541                | 66.26        |
| [7, 8[         | 763       | 4.03  | 13304                | 70.29        |
| [8, 9[         | 602       | 3.18  | 13906                | 73.47        |
| [9, 10]        | 514       | 2.72  | 14420                | 76.18        |
| [10, 11]       | 460       | 2.43  | 14880                | 78.61        |
| [11, 12]       | 399       | 2.11  | 15279                | 80.72        |
| [12, 13]       | 368       | 1.94  | 15647                | 82.67        |
| [13, 17]       | 1136      | 6.00  | 16783                | 88.67        |
| [17, 21]       | 899       | 4.75  | 17682                | 93.42        |
| [21, 25]       | 617       | 3.26  | 18299                | 96.68        |
| [25, 29]       | 359       | 1.90  | 18658                | 98.57        |
| [29, 33]       | 190       | 1.00  | 18848                | 99.58        |
| [33, 37]       | 71        | 0.38  | 18919                | 99.95        |
| ≥ 37           | 9         | 0.05  | 18928                | 100.00       |
| Missing        | 0         | 0.00  | 18928                | 100.00       |
eTable 21: Distribution of follow-up time (expressed in 90-day intervals) for patients continuously exposed to human-only insulin therapy in the primary CVA analyses (all sites combined).

| Follow-up time | Frequency | %     | Cumulative Frequency | Cumulative % |
|----------------|-----------|-------|----------------------|--------------|
| [1, 2]         | 8942      | 8.23  | 8942                 | 8.23         |
| [2, 3]         | 7034      | 6.47  | 15976                | 14.70        |
| [3, 4]         | 34300     | 31.56 | 50276                | 46.26        |
| [4, 5]         | 10621     | 9.77  | 60897                | 56.04        |
| [5, 6]         | 6133      | 5.64  | 67030                | 61.68        |
| [6, 7]         | 5307      | 4.88  | 72337                | 66.56        |
| [7, 8]         | 4506      | 4.15  | 76843                | 70.71        |
| [8, 9]         | 3877      | 3.57  | 80720                | 74.28        |
| [9, 10]        | 3055      | 2.81  | 83775                | 77.09        |
| [10, 11]       | 2741      | 2.52  | 86516                | 79.61        |
| [11, 12]       | 2402      | 2.21  | 88918                | 81.82        |
| [12, 13]       | 2166      | 1.99  | 91084                | 83.82        |
| [13, 17]       | 5975      | 5.50  | 97059                | 89.31        |
| [17, 21]       | 4122      | 3.79  | 101181               | 93.11        |
| [21, 25]       | 2917      | 2.68  | 104098               | 95.79        |
| [25, 29]       | 2384      | 2.19  | 106482               | 97.98        |
| [29, 33]       | 1289      | 1.19  | 107771               | 99.17        |
| [33, 37]       | 799       | 0.74  | 108570               | 99.91        |
| ≥ 37           | 102       | 0.09  | 108672               | 100.00       |
| Missing        | 0         | 0.00  | 108672               | 100.00       |

eTable 22: Summary statistics of the distribution of follow-up time (expressed in 90-day intervals) by exposure regimen in the primary CVA analyses (all sites combined).

| Exposure | N    | Min. | 1st Qu. | Median | Mean  | 3rd Qu. | Max. |
|----------|------|------|---------|--------|-------|---------|------|
| Analog   | 18928| 1    | 3       | 4      | 6.96  | 9       | 37   |
| Human    | 108672| 1    | 3       | 4      | 7.01  | 9       | 37   |
eTable 23: Distribution of follow-up time (expressed in 90-day intervals) for patients continuously exposed to analog-containing insulin therapy in the primary CVD mortality analyses (all sites combined).

| Follow-up time | Frequency | %    | Cumulative Frequency | Cumulative % |
|----------------|-----------|------|----------------------|--------------|
| 1, 2           | 1800      | 10.95| 1800                 | 10.95        |
| 2, 3           | 1129      | 6.87 | 2929                 | 17.81        |
| 3, 4           | 4920      | 29.92| 7849                 | 47.73        |
| 4, 5           | 1465      | 8.91 | 9314                 | 56.64        |
| 5, 6           | 875       | 5.32 | 10189                | 61.97        |
| 6, 7           | 792       | 4.82 | 10981                | 66.78        |
| 7, 8           | 671       | 4.08 | 11652                | 70.86        |
| 8, 9           | 572       | 3.48 | 12224                | 74.34        |
| 9, 10          | 501       | 3.05 | 12725                | 77.39        |
| 10, 11         | 457       | 2.78 | 13182                | 80.17        |
| 11, 12         | 440       | 2.68 | 13622                | 82.84        |
| 12, 13         | 414       | 2.52 | 14036                | 85.36        |
| 13, 17         | 1231      | 7.49 | 15267                | 92.85        |
| 17, 21         | 697       | 4.24 | 15964                | 97.09        |
| 21, 25         | 331       | 2.01 | 16295                | 99.10        |
| 25, 29         | 137       | 0.83 | 16432                | 99.93        |
| ≥ 29           | 11        | 0.07 | 16443                | 100.00       |
| Missing        | 0         | 0.00 | 16443                | 100.00       |
eTable 24: Distribution of follow-up time (expressed in 90-day intervals) for patients continuously exposed to human-only insulin therapy in the primary CVD mortality analyses (all sites combined).

| Follow-up time | Frequency | %    | Cumulative Frequency | Cumulative % |
|----------------|-----------|------|----------------------|--------------|
| [1, 2]         | 7781      | 9.87 | 7781                 | 9.87         |
| [2, 3]         | 6146      | 7.79 | 13927                | 17.66        |
| [3, 4]         | 25048     | 31.76| 38975                | 49.42        |
| [4, 5]         | 7629      | 9.67 | 46604                | 59.10        |
| [5, 6]         | 4313      | 5.47 | 50917                | 64.57        |
| [6, 7]         | 3757      | 4.76 | 54674                | 69.33        |
| [7, 8]         | 3105      | 3.94 | 57779                | 73.27        |
| [8, 9]         | 2688      | 3.41 | 60467                | 76.68        |
| [9, 10]        | 2109      | 2.67 | 62576                | 79.35        |
| [10, 11]       | 1789      | 2.27 | 64365                | 81.62        |
| [11, 12]       | 1707      | 2.16 | 66072                | 83.79        |
| [12, 13]       | 1556      | 1.97 | 67628                | 85.76        |
| [13, 17]       | 4578      | 5.81 | 72206                | 91.57        |
| [17, 21]       | 3545      | 4.50 | 75751                | 96.06        |
| [21, 25]       | 1831      | 2.32 | 77582                | 98.38        |
| [25, 29]       | 1158      | 1.47 | 78740                | 99.85        |
| ≥ 29           | 117       | 0.15 | 78857                | 100.00       |
| Missing        | 0         | 0.00 | 78857                | 100.00       |

eTable 25: Summary statistics of the distribution of follow-up time (expressed in 90-day intervals) by exposure regimen in the primary CVD mortality analyses (all sites combined).

| Exposure | N     | Min. | 1st Qu. | Median | Mean   | 3rd Qu. | Max. |
|----------|-------|------|---------|--------|--------|---------|------|
| Analog   | 16443 | 1    | 3       | 4      | 6.31   | 9       | 29   |
| Human    | 78857 | 1    | 3       | 4      | 6.26   | 8       | 29   |
eTable 26: Distribution of follow-up time (expressed in 90-day intervals) for patients continuously exposed to analog-containing insulin therapy in the primary all-cause mortality analyses (all sites combined).

| Follow-up time | Frequency | %     | Cumulative Frequency | Cumulative % |
|----------------|-----------|-------|----------------------|--------------|
| [1, 2]         | 1904      | 10.06 | 1904                 | 10.06        |
| [2, 3]         | 1198      | 6.33  | 3102                 | 16.39        |
| [3, 4]         | 5861      | 30.96 | 8963                 | 47.35        |
| [4, 5]         | 1674      | 8.84  | 10637                | 56.20        |
| [5, 6]         | 1004      | 5.30  | 11641                | 61.50        |
| [6, 7]         | 856       | 4.52  | 12497                | 66.02        |
| [7, 8]         | 760       | 4.02  | 13257                | 70.04        |
| [8, 9]         | 608       | 3.21  | 13865                | 73.25        |
| [9, 10]        | 519       | 2.74  | 14384                | 75.99        |
| [10, 11]       | 457       | 2.41  | 14841                | 78.41        |
| [11, 12]       | 397       | 2.10  | 15238                | 80.51        |
| [12, 13]       | 374       | 1.98  | 15612                | 82.48        |
| [13, 17]       | 1138      | 6.01  | 16750                | 88.49        |
| [17, 21]       | 904       | 4.78  | 17654                | 93.27        |
| [21, 25]       | 634       | 3.35  | 18288                | 96.62        |
| [25, 29]       | 360       | 1.90  | 18648                | 98.52        |
| [29, 33]       | 197       | 1.04  | 18845                | 99.56        |
| [33, 37]       | 73        | 0.39  | 18918                | 99.95        |
| ≥ 37           | 10        | 0.05  | 18928                | 100.00       |
| Missing        | 0         | 0.00  | 18928                | 100.00       |
Table 27: Distribution of follow-up time (expressed in 90-day intervals) for patients continuously exposed to human-only insulin therapy in the primary all-cause mortality analyses (all sites combined).

| Follow-up time | Frequency | %  | Cumulative Frequency | Cumulative % |
|----------------|-----------|----|----------------------|--------------|
| [1, 2]         | 8738      | 8.04| 8738                 | 8.04         |
| [2, 3]         | 6954      | 6.40| 15692                | 14.44        |
| [3, 4]         | 34352     | 31.61| 50044               | 46.05        |
| [4, 5]         | 10648     | 9.80| 60692                | 55.85        |
| [5, 6]         | 6142      | 5.65| 66834                | 61.50        |
| [6, 7]         | 5317      | 4.89| 72151                | 66.39        |
| [7, 8]         | 4521      | 4.16| 76672                | 70.55        |
| [8, 9]         | 3862      | 3.55| 80534                | 74.11        |
| [9, 10]        | 3053      | 2.81| 83587                | 76.92        |
| [10, 11]       | 2737      | 2.52| 86324                | 79.44        |
| [11, 12]       | 2410      | 2.22| 88734                | 81.65        |
| [12, 13]       | 2166      | 1.99| 90900                | 83.65        |
| [13, 17]       | 5993      | 5.51| 96893                | 89.16        |
| [17, 21]       | 4152      | 3.82| 101045               | 92.98        |
| [21, 25]       | 2960      | 2.72| 104005               | 95.71        |
| [25, 29]       | 2421      | 2.23| 106426               | 97.93        |
| [29, 33]       | 1323      | 1.22| 107749               | 99.15        |
| [33, 37]       | 818       | 0.75| 108567               | 99.90        |
| ≥ 37           | 105       | 0.10| 108672               | 100.00       |
| Missing        | 0         | 0.00| 108672               | 100.00       |

Table 28: Summary statistics of the distribution of follow-up time (expressed in 90-day intervals) by exposure regimen in the primary all-cause mortality analyses (all sites combined).

| Exposure | N     | Min. | 1st Qu. | Median | Mean | 3rd Qu. | Max. |
|----------|-------|------|---------|--------|------|---------|------|
| Analog   | 18928 | 1    | 3       | 4      | 7.01 | 9       | 37   |
| Human    | 108672| 1    | 3       | 4      | 7.05 | 9       | 37   |

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Table 29: AMI results. The reference exposure regimen is “continuous exposure to human-only insulin therapy”.

| Analysis                  | PS estimation    | HR      | AUC     | RD1                      | RD2                      |
|---------------------------|------------------|---------|---------|--------------------------|--------------------------|
| Primary                   | Crude (no weight)| 1.1008 [0.9341;1.2675] | 0.372    | 0.001 [-9e-04;0.0029]   | 5e-04 [-0.0025;0.0036] |
|                           |                  | SE=0.0851, p=0.236 |         | SE=0.001, p=0.301       | SE=0.0015, p=0.726       |
|                           | Logistic 1       | 1.2153 [0.9794;1.4512] | 0.086    | 0.0019 [-8e-04;0.0045]  | 0.0035 [-0.0011;0.008]  |
|                           |                  | SE=0.1203, p=0.074 |         | SE=0.0014, p=0.176      | SE=0.0002, p=0.14        |
|                           | Logistic 2       | 1.079 [0.8579;1.3]  | 0.594    | 4e-04 [-0.0021;0.0029]  | 8e-04 [-0.0035;0.0052]  |
|                           |                  | SE=0.1128, p=0.484 |         | SE=0.0013, p=0.726      | SE=0.0022, p=0.705       |
|                           | Logistic 3       | 1.1052 [0.7639;1.4464] | 0.889    | -0.0014 [-0.0039;0.0011] | -5e-04 [-0.0055;0.0045] |
|                           |                  | SE=0.1741, p=0.546 |         | SE=0.0013, p=0.26       | SE=0.0026, p=0.853       |
|                           | SL               | 1.1085 [0.7665;1.4505] | 0.87     | -0.0015 [-0.004;0.001]  | -4e-04 [-0.0054;0.0046] |
|                           |                  | SE=0.1745, p=0.534 |         | SE=0.0013, p=0.252      | SE=0.0026, p=0.889       |
| Sensitivity 1             | Crude (no weight)| 1.065 [0.9208;1.2092] | 0.498    | 7e-04 [-0.001;0.0023]   | 4e-04 [-0.0023;0.003]   |
|                           |                  | SE=0.0736, p=0.377 |         | SE=8e-04, p=0.41        | SE=0.0013, p=0.793       |
|                           | Logistic 1       | 1.1298 [0.9373;1.3222] | 0.27     | 0.0014 [-9e-04;0.0038]  | 0.0016 [-0.0019;0.0052] |
|                           |                  | SE=0.0982, p=0.186 |         | SE=0.0012, p=0.226      | SE=0.0018, p=0.368       |
|                           | Logistic 2       | 1.0111 [0.8319;1.1902] | 0.81     | 2e-04 [-0.002;0.0024]   | -9e-04 [-0.0042;0.0025] |
|                           |                  | SE=0.0914, p=0.904 |         | SE=0.0011, p=0.842      | SE=0.0017, p=0.62        |
|                           | Logistic 3       | 1.0336 [0.7842;1.2829] | 0.892    | -6e-04 [-0.0031;0.0019] | -9e-04 [-0.0052;0.0028] |
|                           |                  | SE=0.1272, p=0.792 |         | SE=0.0013, p=0.637      | SE=0.0002, p=0.563       |
|                           | SL               | 1.0325 [0.7829;1.2821] | 0.892    | -6e-04 [-0.0031;0.0019] | -9e-04 [-0.0051;0.0029] |
|                           |                  | SE=0.1274, p=0.798 |         | SE=0.0013, p=0.625      | SE=0.0002, p=0.58        |
| Sensitivity 2             | Crude (no weight)| 1.1665 [0.9264;1.4065] | 0.411    | 0.0012 [-0.0011;0.0036] | 5e-04 [-0.0033;0.0042] |
|                           |                  | SE=0.1225, p=0.174 |         | SE=0.0012, p=0.312      | SE=0.0019, p=0.809       |
|                           | Logistic 1       | 1.3087 [0.9737;1.6437] | 0.18     | 0.0023 [-9e-04;0.0056]  | 0.0015 [-0.0032;0.0063] |
|                           |                  | SE=0.1709, p=0.071 |         | SE=0.0017, p=0.157      | SE=0.0024, p=0.528       |
|                           | Logistic 2       | 1.1865 [0.865;1.5079] | 0.538    | 0.0014 [-0.0018;0.0046] | -2e-04 [-0.0052;0.0048] |
|                           |                  | SE=0.164, p=0.256 |         | SE=0.0016, p=0.386      | SE=0.0026, p=0.938       |
|                           | Logistic 3       | 1.1074 [0.7554;1.4594] | 0.895    | 1e-04 [-0.0031;0.0032]  | -9e-04 [-0.0069;0.0038] |
|                           |                  | SE=0.1796, p=0.55 |         | SE=0.0016, p=0.974      | SE=0.0027, p=0.568       |
|                           | SL               | 1.1063 [0.7563;1.4563] | 0.888    | 0 [-0.0031;0.0032]      | -9e-04 [-0.0068;0.0037] |
|                           |                  | SE=0.1786, p=0.552 |         | SE=0.0016, p=0.981      | SE=0.0027, p=0.564       |
| Sensitivity 3             | Crude (no weight)| 1.123 [0.9439;1.302] | 0.281    | 0.0011 [-9e-04;0.0032]  | 0.0011 [-0.0022;0.0044] |
|                           |                  | SE=0.0914, p=0.178 |         | SE=0.0011, p=0.278      | SE=0.0017, p=0.505       |
|                           | Logistic 1       | 1.2624 [1.0223;1.5025] | 0.046    | 0.0022 [-5e-04;0.0048]  | 0.0039 [-7e-04;0.0086] |
|                           |                  | SE=0.1225, p=0.032 |         | SE=0.0014, p=0.111      | SE=0.0024, p=0.989       |
|                           | Logistic 2       | 1.1208 [0.8941;1.3474] | 0.398    | 8e-04 [-0.0017;0.0033]  | 0.0014 [-0.0031;0.0058] |
|                           |                  | SE=0.1157, p=0.296 |         | SE=0.0013, p=0.534      | SE=0.0023, p=0.551       |
|                           | Logistic 3       | 1.1572 [0.7908;1.5236] | 0.701    | -0.0011 [-0.0036;0.0014] | -1e-04 [-0.0051;0.005]  |
|                           |                  | SE=0.1869, p=0.4 |         | SE=0.0013, p=0.374      | SE=0.0026, p=0.977       |
|                           | SL               | 1.1607 [0.7907;1.5306] | 0.687    | -0.0012 [-0.0036;0.0013] | 0 [-0.005;0.0051]       |
|                           |                  | SE=0.1888, p=0.395 |         | SE=0.0013, p=0.362      | SE=0.0026, p=0.996       |
## Table 30: CHF results. The reference exposure regimen is “continuous exposure to human-only insulin therapy”.

| Analysis | PS estimation | HR (SE, p-value) | AUC (SE, p-value) | RD1 (SE, p-value) | RD2 (SE, p-value) |
|----------|---------------|------------------|------------------|------------------|------------------|
| Primary  | Crude (no weight) | 1.1052 [0.9851;1.2252] | 0.132 | 0.0016 [-0.001;0.0041] | 0.0012 [-0.0027;0.0051] |
|          | all sites, 180-day prescription duration | Logistic 1 | 1.0704 [0.9226;1.2182] | 0.634 | 0.0011 [-0.0023;0.0046] | -0.0016 [-0.0068;0.0036] |
|          |             | Logistic 2 | 0.9763 [0.8336;1.119] | 0.469 | -0.0011 [-0.0045;0.0023] | -0.0042 [-0.0092;9e-04] |
|          |             | Logistic 3 | 0.9343 [0.7492;1.1193] | 0.346 | -0.0019 [-0.0063;0.0026] | -0.005 [-0.0112;0.0013] |
|          | SL | 0.9305 [0.7462;1.1149] | 0.319 | -0.002 [-0.0064;0.0025] | -0.0052 [-0.0114;0.0011] |
| Sensitivity 1 | Crude (no weight) | 1.1185 [1.0092;1.2278] | 0.023 | 0.0024 [0;0.0048] | 0.0029 [-6e-04;0.0064] |
|          | all sites, 365-day prescription duration | Logistic 1 | 1.1074 [0.9677;1.2471] | 0.112 | 0.0032 [-2e-04;0.0066] | 0.0024 [-0.0025;0.0074] |
|          |             | Logistic 2 | 1.0111 [0.8778;1.1443] | 0.908 | 7e-04 [-0.0026;0.0039] | -6e-04 [-0.0052;0.0004] |
|          |             | Logistic 3 | 0.957 [0.7807;1.1332] | 0.594 | -1e-04 [-0.0047;0.0045] | -0.0023 [-0.0081;0.0035] |
|          | SL | 0.9531 [0.7778;1.1284] | 0.563 | -1e-04 [-0.0048;0.0045] | -0.0025 [-0.0083;0.0033] |
| Sensitivity 2 | Crude (no weight) | 1.007 [0.8637;1.1504] | 0.798 | 8e-04 [-0.0027;0.0042] | -0.0043 [-0.0092;7e-04] |
|          | Single site with most variability in baseline insulin therapy over time, 180-day prescription duration | Logistic 1 | 0.9851 [0.811;1.1593] | 0.353 | 4e-04 [-0.0042;0.0051] | -0.0084 [-0.0143;0.0025] |
|          |             | Logistic 2 | 0.886 [0.7247;1.0473] | 0.035 | -0.0026 [-0.0071;0.0019] | -0.0109 [-0.0166;0.0051] |
|          |             | Logistic 3 | 0.8303 [0.6557;1.0049] | 0.019 | -0.0031 [-0.0084;0.0022] | -0.0118 [-0.0182;0.0054] |
|          | SL | 0.8245 [0.6518;0.9971] | 0.014 | -0.0033 [-0.0085;0.0019] | -0.0121 [-0.0185;0.0057] |
| Sensitivity 3 | Crude (no weight) | 1.1275 [0.9986;1.2564] | 0.093 | 0.0024 [-3e-04;0.0052] | 9e-04 [-0.0031;0.005] |
|          | Site favoring analog-containing insulin at index excluded, 180-day prescription duration | Logistic 1 | 1.0865 [0.936;1.2371] | 0.517 | 0.0014 [-0.0021;0.0048] | -0.0013 [-0.0065;0.0039] |
|          |             | Logistic 2 | 0.9871 [0.842;1.1322] | 0.562 | -8e-04 [-0.0043;0.0026] | -0.0042 [-0.0092;8e-04] |
|          |             | Logistic 3 | 0.9371 [0.7417;1.1324] | 0.358 | -0.0016 [-0.0062;0.0031] | -0.0056 [-0.012;8e-04] |
|          | SL | 0.9333 [0.7388;1.1278] | 0.333 | -0.0016 [-0.0063;0.003] | -0.0058 [-0.0121;6e-04] |

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| Analysis                  | PS estimation     | HR       | AUC   | RD1          | RD2          |
|--------------------------|-------------------|----------|-------|--------------|--------------|
| **Primary**              |                   |          |       |              |              |
| all sites, 180-day       |                   |          |       |              |              |
| prescription duration    |                   |          |       |              |              |
| Logistic 1               |                   | 1.1912   | 0.134 | 0.0019 [-6e-04;0.0045] | 0.0027 [-0.0011;0.0065] |
|                         |                   | 1.3337   | 0.153 | 0.0013, p=0.135 | 0.0019, p=0.171 |
| Logistic 2               |                   | 1.0725   | 0.533 | 8e-04 [-0.0016;0.0031] | 0.0017 [-0.0022;0.0055] |
|                         |                   | 1.264    | 0.566 | 0.0012, p=0.514 | 0.0002, p=0.402 |
| Logistic 3               |                   | 1.3021   | 0.241 | 0.0035 [-0.0024;0.0094] | 0.0044 [-0.0026;0.0115] |
| SL                      |                   | 1.2969   | 0.247 | 0.0035 [-0.0024;0.0093] | 0.0043 [-0.0027;0.0113] |
| **Sensitivity 1**        |                   |          |       |              |              |
| all sites, 365-day       |                   |          |       |              |              |
| prescription duration    |                   |          |       |              |              |
| Logistic 1               |                   | 1.1129   | 0.207 | 0.0017 [-6e-04;0.0041] | 0.0019 [-0.0015;0.0052] |
|                         |                   | 0.113    | 0.317 | 0.0012, p=0.143 | 0.0017, p=0.274 |
| Logistic 2               |                   | 1.0315   | 0.607 | 8e-04 [-0.0014;0.0003] | 0.0011 [-0.0023;0.0044] |
|                         |                   | 0.1082   | 0.771 | 0.0011, p=0.49 | 0.0017, p=0.531 |
| Logistic 3               |                   | 1.1723   | 0.32  | 0.0024 [-0.0017;0.0066] | 0.0027 [-0.0025;0.0078] |
| SL                      |                   | 1.1653   | 0.334 | 0.0024 [-0.0017;0.0065] | 0.0026 [-0.0026;0.0077] |
| **Sensitivity 2**        |                   |          |       |              |              |
| Single site with the     |                   |          |       |              |              |
| most variability in      |                   |          |       |              |              |
| baseline insulin therapy  |                   |          |       |              |              |
| over time, 180-day       |                   |          |       |              |              |
| prescription duration    |                   |          |       |              |              |
| Logistic 1               |                   | 1.103    | 0.297 | 0.0016 [-0.0014;0.0045] | 0.0025 [-0.0021;0.0007] |
|                         |                   | 0.1473   | 0.484 | 0.0015, p=0.292 | 0.0023, p=0.29 |
| Logistic 2               |                   | 1.0367   | 0.624 | 0.0001 [-0.0002;0.0039] | 0.0016 [-0.0033;0.0065] |
|                         |                   | 0.1433   | 0.815 | 0.0015, p=0.514 | 0.0025, p=0.53 |
| Logistic 3               |                   | 1.1008   | 0.659 | 0.0023 [-0.0055;0.0102] | 0.0023 [-0.0067;0.0113] |
| SL                      |                   | 1.1019   | 0.658 | 0.0023 [-0.0055;0.0102] | 0.0022 [-0.0068;0.0112] |
| **Sensitivity 3**        |                   |          |       |              |              |
| Site favoring analog     |                   |          |       |              |              |
| containing insulin       |                   |          |       |              |              |
| at index excluded,       |                   |          |       |              |              |
| 180-day prescription     |                   |          |       |              |              |
| duration                |                   |          |       |              |              |
| Logistic 1               |                   | 1.2056   | 0.11  | 0.0021 [-6e-04;0.0046] | 0.0029 [-0.001;0.0068] |
|                         |                   | 0.1368   | 0.133 | 0.0013, p=0.109 | 0.0002, p=0.144 |
| Logistic 2               |                   | 1.0833   | 0.463 | 0.001 [-0.0014;0.0033] | 0.0019 [-0.0002;0.0059] |
|                         |                   | 0.1294   | 0.52  | 0.0012, p=0.425 | 0.0002, p=0.345 |
| Logistic 3               |                   | 1.3351   | 0.215 | 0.0039 [-0.0023;0.01] | 0.0049 [-0.0024;0.0122] |
| SL                      |                   | 1.3324   | 0.219 | 0.0039 [-0.0023;0.01] | 0.0048 [-0.0025;0.0121] |

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eTable 32: CVD mortality results. The reference exposure regimen is “continuous exposure to human-only insulin therapy”.

| Analysis                              | PS estimation       | HR            | AUC       | RD1                  | RD2                  |
|---------------------------------------|---------------------|---------------|-----------|----------------------|----------------------|
| Primary                               | Crude (no weight)   | 0.9666 [0.8277;1.1054] | 0.438 | 4e-04 [-0.002;0.0029] | -0.0032 [-0.0067;2e-04] |
|                                       | Logistic 1          | 1.1019 [0.9065;1.2972] | 0.569 | 0.0025 [-0.0014;0.0063] | -0.0015 [-0.007;0.004] |
| all sites, 180-day prescription duration | Logistic 2       | 0.9773 [0.7948;1.1597] | 0.633 | 9e-04 [-0.003;0.0047] | -0.0039 [-0.01;0.0023] |
|                                       | Logistic 3          | 1.2624 [0.8637;1.6611] | 0.22  | 0.0095 [-6e-04;0.0196] | 0.0035 [-0.0074;0.0145] |
|                                       | SL                  | 1.2599 [0.8619;1.6578] | 0.226 | 0.0094 [-7e-04;0.0195] | 0.0034 [-0.0075;0.0144] |
| Sensitivity 1                         | Crude (no weight)   | 0.9503 [0.8289;1.0717] | 0.445 | 1e-04 [-0.0021;0.0024] | -0.0022 [-0.0054;0.001] |
| all sites, 365-day prescription duration | Logistic 1       | 1.0811 [0.905;1.2572] | 0.343 | 0.0026 [-9e-04;0.0061] | 0.0016 [-0.0039;0.0071] |
|                                       | Logistic 2          | 0.9579 [0.7803;1.1356] | 0.726 | 4e-04 [-0.003;0.0038] | -0.0021 [-0.0087;0.0045] |
|                                       | Logistic 3          | 1.202 [0.8787;1.5253] | 0.188 | 0.0061 [-7e-04;0.0129] | 0.0047 [-0.0055;0.0148] |
|                                       | SL                  | 1.1972 [0.8789;1.5155] | 0.193 | 0.0061 [-7e-04;0.0129] | 0.0044 [-0.0053;0.0142] |
| Sensitivity 2                         | Crude (no weight)   | 0.8253 [0.6675;0.9831] | 0.011 | -0.0022 [-0.0051;8e-04] | -0.0075 [-0.0121;0.003] |
| Single site with most variability in baseline insulin therapy over time, 180-day prescription duration | Logistic 1 | 0.9277 [0.7139;1.1416] | 0.18  | -0.001 [-0.005;0.0031] | -0.0074 [-0.0138;-0.001] |
|                                       | Logistic 2          | 0.8454 [0.6397;1.051] | 0.108 | -8e-04 [-0.0058;0.0042] | -0.0089 [-0.0162;0.0015] |
|                                       | Logistic 3          | 0.9773 [0.5834;1.3711] | 0.835 | 0.0039 [-0.0071;0.0148] | -0.0054 [-0.0171;0.0064] |
|                                       | SL                  | 0.9675 [0.5808;1.3543] | 0.782 | 0.0035 [-0.0071;0.0142] | -0.0058 [-0.0173;0.0058] |
| Sensitivity 3                         | Crude (no weight)   | 0.9734 [0.8265;1.1202] | 0.424 | 1e-04 [-0.0024;0.0026] | -0.0033 [-0.0073;0.004] |
| Site favoring analog-containing insulin at index excluded, 180-day prescription duration | Logistic 1 | 1.0997 [0.9038;1.2955] | 0.58  | 0.0026 [-0.0013;0.0064] | -0.0016 [-0.007;0.0039] |
|                                       | Logistic 2          | 0.9773 [0.7935;1.1611] | 0.632 | 0.001 [-0.0028;0.0048] | -0.0039 [-0.0101;0.0022] |
|                                       | Logistic 3          | 1.2789 [0.8533;1.7045] | 0.223 | 0.0101 [-8e-04;0.0211] | 0.0039 [-0.0079;0.0157] |
|                                       | SL                  | 1.2776 [0.8522;1.703] | 0.227 | 0.0101 [-9e-04;0.021] | 0.0038 [-0.0079;0.0156] |

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Table 3: All-cause mortality results. The reference exposure regimen is “continuous exposure to human-only insulin therapy”.

| Analysis | PS estimation | HR | AUC | RD1 | RD2 |
|----------|---------------|----|-----|-----|-----|
| **Primary** | Crude (no weight) | 1.1411 [1.0478;1.2345] | 0.003 | 0.0048 [0.0013;0.0082] | 0.0054 [3e-04;0.0105] |
| all sites, 180-day prescription duration | Logistic 1 | 1.1723 [1.0471;1.2976] | 0.024 | 0.0058 [9e-04;0.0107] | 0.0038 [-0.003;0.0106] |
| | Logistic 2 | 1.0597 [0.9412;1.1782] | 0.477 | 0.0017 [-0.0032;0.0067] | 0.001 [-0.0071;0.0091] |
| | Logistic 3 | 1.1584 [0.9705;1.3462] | 0.125 | 0.0083 [-0.004;0.0172] | 0.006 [-0.0052;0.0172] |
| SL | 1.1526 [0.9665;1.3387] | 0.142 | 0.008 [-0.004;0.0169] | 0.0054 [-0.0056;0.0164] |
| **Sensitivity 1** | Crude (no weight) | 1.1411 [1.0593;1.223] | 0 | 0.0049 [0.0018;0.0081] | 0.0074 [0.0028;0.012] |
| all sites, 365-day prescription duration | Logistic 1 | 1.1572 [1.0498;1.2646] | 0.002 | 0.0065 [0.002;0.0109] | 0.0078 [0.0017;0.014] |
| | Logistic 2 | 1.0429 [0.9429;1.1428] | 0.314 | 0.0018 [-0.0025;0.0061] | 0.0029 [-0.0035;0.0094] |
| | Logistic 3 | 1.1129 [0.9621;1.2637] | 0.099 | 0.0064 [-0.004;0.0132] | 0.0064 [-0.0023;0.0151] |
| SL | 1.1085 [0.9589;1.2581] | 0.112 | 0.0062 [-0.004;0.013] | 0.006 [-0.0026;0.0146] |
| **Sensitivity 2** | Crude (no weight) | 1.0387 [0.92;1.1574] | 0.56 | 8e-04 [-0.0034;0.005] | 0.0016 [-0.0047;0.008] |
| Single site with most variability in baseline insulin therapy over time, 180-day prescription duration | Logistic 1 | 1.1595 [0.9941;1.3249] | 0.095 | 0.0047 [-0.0012;0.0105] | 0.0055 [-0.003;0.0139] |
| | Logistic 2 | 1.0693 [0.9082;1.2303] | 0.498 | 0.0015 [-0.0044;0.0075] | 0.0025 [-0.0079;0.0129] |
| | Logistic 3 | 1.1853 [0.9164;1.4542] | 0.218 | 0.0082 [-0.0042;0.0206] | 0.0075 [-0.0085;0.0235] |
| SL | 1.1829 [0.916;1.4499] | 0.225 | 0.0082 [-0.0043;0.0206] | 0.0073 [-0.0083;0.0229] |
| **Sensitivity 3** | Crude (no weight) | 1.0909 [0.9943;1.1875] | 0.105 | 0.0032 [-2e-04;0.0067] | 0.0022 [-0.003;0.0075] |
| Site favoring analog-containing insulin at index excluded, 180-day prescription duration | Logistic 1 | 1.1829 [1.0561;1.3098] | 0.018 | 0.006 [0.0012;0.0109] | 0.004 [-0.0028;0.0107] |
| | Logistic 2 | 1.0672 [0.9471;1.1872] | 0.44 | 0.0018 [-0.003;0.0067] | 0.0012 [-0.0069;0.0093] |
| | Logistic 3 | 1.1584 [0.963;1.3537] | 0.147 | 0.0082 [-0.0011;0.0176] | 0.0059 [-0.0058;0.0177] |
| SL | 1.1514 [0.9583;1.3445] | 0.167 | 0.0079 [-0.0013;0.0171] | 0.0053 [-0.0062;0.0167] |
eTable 34: Summary statistics of the inverse probability weights (IPW) involved in the AMI analyses.

| Analysis                  | PS estimation | 99<sup>th</sup> percentile | 99.99<sup>th</sup> percentile | Maximum          | Percentage of IPW ≥ 20 |
|---------------------------|---------------|-----------------------------|-------------------------------|------------------|------------------------|
| Primary                   |               |                             |                               |                  |                        |
| Logistic 1                | 2.88          | 8.51                        | 226.08                        | 0.02             |
| Logistic 2                | 4.77          | 24.51                       | 793182.22                     | 0.12             |
| Logistic 3                | 5.27          | 26.53                       | 403173.85                     | 0.15             |
| SL                        | 4.95          | 23.36                       | 206848.68                     | 0.12             |
| Sensitivity 1             |               |                             |                               |                  |                        |
| (365) Logistic 1          | 2.99          | 9.42                        | 341.97                        | 0.03             |
| Logistic 2                | 4.94          | 22.43                       | 2564.02                       | 0.12             |
| Logistic 3                | 5.54          | 25.23                       | 2225.97                       | 0.14             |
| SL                        | 5.12          | 21.77                       | 1962.56                       | 0.11             |
| Sensitivity 2             |               |                             |                               |                  |                        |
| (single site) Logistic 1  | 3.09          | 6.77                        | 104.88                        | 0.01             |
| Logistic 2                | 4.78          | 24.40                       | 104729.23                     | 0.12             |
| Logistic 3                | 5.42          | 29.01                       | 99615.08                      | 0.16             |
| SL                        | 5.04          | 24.99                       | 73964.02                      | 0.13             |
| Sensitivity 3             |               |                             |                               |                  |                        |
| (one site excluded) Logistic 1 | 2.84        | 7.27                        | 202.45                        | 0.01             |
| Logistic 2                | 4.70          | 22.37                       | 859583.30                     | 0.11             |
| Logistic 3                | 5.24          | 24.26                       | 430850.17                     | 0.13             |
| SL                        | 4.91          | 21.37                       | 230787.13                     | 0.11             |
eTable 35: Summary statistics of the inverse probability weights (IPW) involved in the CHF analyses.

| Analysis                     | PS estimation | 99<sup>th</sup> percentile | 99.99<sup>th</sup> percentile | Maximum       | Percentage of IPW ≥ 20 |
|------------------------------|---------------|-------------------------------|-------------------------------|---------------|------------------------|
| Primary                      |               |                               |                               |               |                        |
| Logistic 1                   | 2.76          | 7.48                          | 182.58                        | 0.02          |
| Logistic 2                   | 4.67          | 20.10                         | 10817.68                      | 0.10          |
| Logistic 3                   | 5.16          | 22.75                         | 10136.96                      | 0.13          |
| SL                           | 4.80          | 20.38                         | 9646.87                       | 0.10          |
| Sensitivity 1 (365)          |               |                               |                               |               |                        |
| Logistic 1                   | 2.84          | 8.27                          | 179.49                        | 0.03          |
| Logistic 2                   | 4.85          | 21.48                         | 3092.48                       | 0.11          |
| Logistic 3                   | 5.42          | 24.15                         | 3474.22                       | 0.13          |
| SL                           | 5.01          | 20.98                         | 3149.91                       | 0.11          |
| Sensitivity 2 (single site)  |               |                               |                               |               |                        |
| Logistic 1                   | 2.94          | 6.15                          | 96.09                         | 0.00          |
| Logistic 2                   | 4.78          | 19.63                         | 545.68                        | 0.10          |
| Logistic 3                   | 5.26          | 24.40                         | 438.06                        | 0.13          |
| SL                           | 4.92          | 20.77                         | 246.44                        | 0.11          |
| Sensitivity 3 (one site excluded) |       |                               |                               |               |                        |
| Logistic 1                   | 2.72          | 6.48                          | 210.50                        | 0.01          |
| Logistic 2                   | 4.60          | 18.52                         | 11734.83                      | 0.09          |
| Logistic 3                   | 5.10          | 21.13                         | 11313.56                      | 0.11          |
| SL                           | 4.77          | 18.68                         | 10696.20                      | 0.09          |

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eTable 36: Summary statistics of the inverse probability weights (IPW) involved in the CVA analyses.

| Analysis           | PS estimation | 99th percentile | 99.99th percentile | Maximum   | Percentage of IPW $\geq 20$ |
|--------------------|---------------|-----------------|--------------------|-----------|-----------------------------|
| **Primary**        |               |                 |                    |           |                             |
| Logistic 1         | 2.92          | 8.34            | 231.74             | 0.03      |                             |
| Logistic 2         | 4.80          | 24.68           | 790421.98          | 0.13      |                             |
| Logistic 3         | 5.29          | 27.03           | 404390.61          | 0.15      |                             |
| SL                 | 4.95          | 23.65           | 200042.19          | 0.12      |                             |
| **Sensitivity 1**  |               |                 |                    |           |                             |
| (365)              |               |                 |                    |           |                             |
| Logistic 1         | 3.01          | 9.28            | 354.40             | 0.03      |                             |
| Logistic 2         | 5.00          | 23.10           | 25531.32           | 0.12      |                             |
| Logistic 3         | 5.59          | 25.63           | 19474.62           | 0.14      |                             |
| SL                 | 5.17          | 22.00           | 15920.99           | 0.12      |                             |
| **Sensitivity 2**  |               |                 |                    |           |                             |
| (single site)      |               |                 |                    |           |                             |
| Logistic 1         | 3.11          | 6.80            | 189.65             | 0.00      |                             |
| Logistic 2         | 4.86          | 25.04           | 118032.18          | 0.13      |                             |
| Logistic 3         | 5.47          | 29.97           | 114610.75          | 0.17      |                             |
| SL                 | 5.09          | 25.66           | 92110.35           | 0.14      |                             |
| **Sensitivity 3**  |               |                 |                    |           |                             |
| (one site excluded)|               |                 |                    |           |                             |
| Logistic 1         | 2.87          | 7.07            | 310.48             | 0.01      |                             |
| Logistic 2         | 4.73          | 22.54           | 860883.03          | 0.11      |                             |
| Logistic 3         | 5.25          | 24.49           | 434861.23          | 0.13      |                             |
| SL                 | 4.91          | 21.44           | 229026.02          | 0.11      |                             |
Table 37: Summary statistics of the inverse probability weights (IPW) involved in the CVD mortality analyses.

| Analysis          | PS estimation | 99th percentile | 99.99th percentile | Maximum  | Percentage of IPW ≥ 20 |
|-------------------|---------------|-----------------|--------------------|----------|------------------------|
| **Primary**       |               |                 |                    |          |                        |
| Logistic 1        | 2.53          | 6.86            | 58.05              | 0.01     |
| Logistic 2        | 4.58          | 20.70           | 1004.69            | 0.10     |
| Logistic 3        | 5.25          | 23.90           | 825.98             | 0.13     |
| SL                | 4.95          | 20.76           | 569.44             | 0.11     |
| **Sensitivity 1 (365)** |               |                 |                    |          |                        |
| Logistic 1        | 2.74          | 7.98            | 73.11              | 0.02     |
| Logistic 2        | 5.04          | 20.18           | 1401.33            | 0.10     |
| Logistic 3        | 5.85          | 23.19           | 1524.98            | 0.12     |
| SL                | 5.49          | 20.49           | 1199.83            | 0.10     |
| **Sensitivity 2 (single site)** |               |                 |                    |          |                        |
| Logistic 1        | 2.55          | 4.87            | 17.91              | 0.00     |
| Logistic 2        | 4.39          | 20.58           | 924.25             | 0.10     |
| Logistic 3        | 5.35          | 23.97           | 882.96             | 0.12     |
| SL                | 5.04          | 20.56           | 459.27             | 0.10     |
| **Sensitivity 3 (one site excluded)** |               |                 |                    |          |                        |
| Logistic 1        | 2.46          | 5.47            | 25.79              | 0.00     |
| Logistic 2        | 4.50          | 18.98           | 992.26             | 0.09     |
| Logistic 3        | 5.18          | 21.87           | 846.68             | 0.12     |
| SL                | 4.87          | 19.38           | 588.49             | 0.09     |
eTable 38: Summary statistics of the inverse probability weights (IPW) involved in the all-cause mortality analyses.

| Analysis        | PS estimation | 99<sup>th</sup> percentile | 99.99<sup>th</sup> percentile | Maximum   | Percentage of IPW ≥ 20 |
|-----------------|---------------|-----------------------------|--------------------------------|-----------|------------------------|
| Primary         |               |                             |                                |           |                        |
| Logistic 1      | 2.48          | 5.72                        | 65.49                          | 0.01      |                        |
| Logistic 2      | 4.09          | 16.80                       | 1116.62                        | 0.08      |                        |
| Logistic 3      | 4.65          | 19.92                       | 1934.06                        | 0.10      |                        |
| SL              | 4.33          | 17.31                       | 1374.05                        | 0.08      |                        |
| Sensitivity 1   |               |                             |                                |           |                        |
| (365)           |               |                             |                                |           |                        |
| Logistic 1      | 2.48          | 5.88                        | 72.65                          | 0.01      |                        |
| Logistic 2      | 4.32          | 16.74                       | 466.03                         | 0.08      |                        |
| Logistic 3      | 4.98          | 21.20                       | 729.87                         | 0.10      |                        |
| SL              | 4.56          | 17.21                       | 709.81                         | 0.08      |                        |
| Sensitivity 2   |               |                             |                                |           |                        |
| (single site)   |               |                             |                                |           |                        |
| Logistic 1      | 2.69          | 5.11                        | 18.38                          | 0.00      |                        |
| Logistic 2      | 4.32          | 16.74                       | 398.01                         | 0.08      |                        |
| Logistic 3      | 4.98          | 22.20                       | 405.55                         | 0.11      |                        |
| SL              | 4.64          | 18.30                       | 166.43                         | 0.09      |                        |
| Sensitivity 3   |               |                             |                                |           |                        |
| (one site excluded) |           |                             |                                |           |                        |
| Logistic 1      | 2.42          | 4.87                        | 52.95                          | 0.00      |                        |
| Logistic 2      | 4.05          | 15.48                       | 965.47                         | 0.07      |                        |
| Logistic 3      | 4.58          | 18.50                       | 1713.45                        | 0.09      |                        |
| SL              | 4.25          | 16.00                       | 1240.14                        | 0.07      |                        |
eFigure 1: Survival curve estimates for AMI (primary and sensitivity analyses). The left plots represent the unadjusted estimates. The right plots represent the truncated IPW estimates based on SL estimation of the propensity scores.
eFigure 2: Survival curve estimates for CHF (primary and sensitivity analyses). The left plots represent the unadjusted estimates. The right plots represent the truncated IPW estimates based on SL estimation of the propensity scores.

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eFigure 3: Survival curve estimates for CVA (primary and sensitivity analyses). The left plots represent the unadjusted estimates. The right plots represent the truncated IPW estimates based on SL estimation of the propensity scores.
eFigure 4: Survival curve estimates for CVD mortality (primary and sensitivity analyses). The left plots represent the unadjusted estimates. The right plots represent the truncated IPW estimates based on SL estimation of the propensity scores.
eFigure 5: Survival curve estimates for all-cause mortality (primary and sensitivity analyses). The left plots represent the unadjusted estimates. The right plots represent the truncated IPW estimates based on SL estimation of the propensity scores.
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