The Association of Long-Acting Insulin Analogue Use Versus Neutral Protamine Hagedorn Insulin Use With Major Adverse Cardiovascular Events Among Individuals With Type 2 Diabetes: A Population-Based Cohort Study

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Supplementary Material

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Supplemental methods 1

Inverse probability of treatment weights (IPTW)

For each person-month of follow-up, we generated stabilized weighted using inverse probability of treatment weights (IPTWs) and inverse probability of censoring weights (IPCWs). IPTWs were used to determine the inverse probability of the observed treatment. We used a logistic model to estimate the numerator of the IPTW, estimating the probability of observed treatment (long-acting insulin analogues versus NPH insulin) conditional on baseline covariates (see **e-Table 1**), previous treatment, and month of follow-up duration. The denominator of the IPTW was estimated using a logistic model, conditional on baseline and time-varying covariates, previous treatment, and month of follow-up duration. For the analyses by individual long-acting insulin analogue type, multinomial logistic regression was used to compute the numerator and the denominator of the IPTW.

Inverse probability of censoring weights (IPCW)

We then constructed two different IPCW models to account for potential differential censoring between exposure groups, according to the reasons for censoring. The first IPCW model ($IPCW_A$) estimated the probability of censoring due to loss to follow-up, end of registration with the CPRD, non-cardiovascular death (except for the outcome of all-cause mortality), or end of the study period (November 30th, 2018). The second IPCW model ($IPCW_B$) estimated the probability of censoring due to either treatment discontinuation or use of both long-acting insulins and NPH. Both IPCWs were estimated using logistic models that were conditioned on baseline covariates, previous treatment, and month of follow-up for the IPCW numerators and baseline and time-varying covariates, previous treatment, and month of follow-up for the IPCW denominators. For

the analyses by individual long-acting insulin analogue type, multinomial logistic regression was used to compute the numerator and the denominator of the IPTW.

We used the product of the IPTW, $IPCW_{A,}$ and $IPCW_B$ to obtain standardized weights. Standardized weights below 1st percentile and 99th percentile were truncated to the values of the 1st and 99th percentiles[1,2], respectively.

The stabilized weights were included in a Cox proportional hazards model with robust variance estimators[3] and adjusted for baseline covariates[1] to estimate marginal HRs and 95% CIs for each outcome of interest, comparing current use of long-acting insulin analogues to NPH. Continuous variables (age, duration of treated diabetes, and month of follow-up time) were modeled using restricted cubic splines with 5 knots (3 interior knots) to account for potential non-linear associations and to decrease the variance of the estimator[4].

Multiple imputation

All variables with missing information (Index of Multiple Deprivation, ethnicity, body mass index [BMI], systolic blood pressure [SBP], diastolic blood pressure [DBP], glycated hemoglobin A1c [HbA1c], and estimated glomerular filtration rate [eGFR]) were imputed using multiple imputation by chained equations[5] prior to estimating the IPTW and IPCWs to ensure that the positivity assumption[6] was met. We used logistic regression to perform 5 independent imputations using variables that can help predict missingness, including exposure, outcome, and covariates[7]. The resulting datasets were analyzed separately. We pooled the estimates and computed standard errors using Rubin's rule [8].

e-Table 1: Description of covariates, their assessment windows, and the models in which they were included.

Characteristic	Description	Baseline lookback	Time varying assessment	IPTW	$IPCW_A$	$IPCW_B$	Outcome model
Demographic							
Age		Defined at cohort entry date	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Sex	women, men	N/A	N/A	yes	yes	yes	yes
Ethnicity	Caucasian, other	N/A	N/A	yes	yes	yes	yes
Index of multiple deprivation quintile	1 (least deprived) to 5 (most deprived)	N/A	N/A	yes	yes	yes	yes
Duration of treated diabetes	Defined as time between the first prescription of	Defined at cohort entry date	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Smoking status	ever/never	anytime prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Clinical measurements							
Body mass index	continuous, kg/m^2	latest measurement in the year prior to cohort entry	updated every 365 days	yes	yes	yes	yes, baseline only
HbA1c	continuous, %	latest measurement in the year prior to cohort entry	updated every 365 days	yes	yes	yes	yes, baseline only
eGFR	continuous, $ml/min/1.73m^2$	latest measurement in	updated every 365 days	yes	yes	yes	yes, baseline only

		the year prior to cohort entry					
Systolic blood pressure	continuous, mmHg	latest measurement in the year prior to cohort entry	updated every 365 days	yes	yes	yes	yes, baseline only
Diastolic blood pressure	continuous, mmHg	latest measurement in the year prior to cohort entry	updated every 365 days	yes	yes	yes	yes, baseline only
Comorbidities							
Alcohol related disorders: alcoholism, cirrhosis, hepatitis, and liver failure	yes/no	anytime prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Atrial fibrillation	yes/no	anytime prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Cancer	other than non-melanoma skin cancer yes/no	anytime prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
COPD	yes/no	anytime prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Coronary artery disease	yes/no	anytime prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Dyslipidemia	yes/no	anytime prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Hypertension	yes/no	anytime prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Peripheral vascular disease	yes/no	anytime prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only

Stroke	yes/no	anytime prior to cohort entry	ever/never, updated at 30-day intervals, except where stroke or MACE is the outcome	yes*	yes	yes	yes, baseline only
MI	yes/no	anytime prior to cohort entry	ever/never, updated at 30-day intervals (except where MI or MACE is the outcome)	yes*	yes	yes	yes, baseline only
Coronary revascularization	yes/no	anytime prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Acute kidney injury	yes/no	anytime prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Chronic kidney disease	yes/no	anytime prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Retinopathy	yes/no	anytime prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Neuropathy	yes/no	anytime prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Dialysis	yes/no	anytime prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Use of antidiabetic drugs							
Metformin	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Sulfonylureas	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Thiazolidinediones	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
DPP-4 inhibitors	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
SGLT-2 inhibitors	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
GLP-1 receptor agonists	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only

Alpha-glucosidase inhibitors	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Meglitinides	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Non-basal insulin	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Use of other drugs							
Angiotensin-converting enzyme inhibitors	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Angiotensin II receptor blockers	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Beta-blockers	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Calcium channel blockers	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Diuretics	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Oral anticoagulants	vitamin K antagonists, direct-acting oral anticoagulants yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Antiplatelets	clopidogrel, ticagrelor, prasugrel yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Statins	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Acetylsalicylic acid	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Nonsteroidal anti-inflammatory drugs	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only

Abbreviations: NPH: neutral protamine Hagedorn, aSD: absolute standardized difference, SD: standard deviation. BMI: body mass index, HbA1c: glycated hemoglobin, eGFR: estimated glomerular filtration rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, COPD: chronic obstructive pulmonary disorder, TZD: thiazolidinediones, DPP-4: dipeptidyl peptidase-4, GLP-1: glucagon-like peptide-1, SGLT-2: sodium-glucose co-transporter 2, ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blockers, DOAC: direct oral anticoagulants, NSAID: non-steroidal anti-inflammatory drugs

e-Table 2: Baseline characteristics of initiators of glargine, detemir, and degludec among patients with type 2 diabetes in the UK.

Characteristic	NPH	Detemir	Glargine	Degludec
N (%)*	26,198 (45.7)	8,368 (14.6)	22,226 (38.8)	437 (0.8)
Female	11,861 (45.3)	3,757 (44.9)	9,538 (42.9)	193 (44.2)
Age, years, mean (SD)	64.4 (14.2)	61.3 (14.5)	64.0 (14.1)	61.5 (13.2)
<40	1,575 (6.0)	643 (7.7)	1,071 (4.8)	26 (5.9)
40 to 49.9	2,408 (9.2)	1,142 (13.6)	2,466 (11.1)	42 (9.6)
50 to 59.9	4,936 (18.8)	1,879 (22.5)	4,700 (21.1)	126 (28.8)
60 to 69.9	6,836 (26.1)	2,079 (24.8)	5,566 (25.0)	123 (28.1)
70 to 79.9	6,841 (26.1)	1,745 (20.9)	5,139 (23.1)	82 (18.8)
80+	3,602 (13.7)	880 (10.5)	3,284 (14.8)	38 (8.7)
Ethnicity				
Caucasian	21,025 (80.3)	6,822 (81.5)	17,803 (80.1)	356 (81.5)
Non-Caucasian	4,081 (15.6)	1,127 (13.5)	3,341 (15.0)	48 (11.0)
Missing	1,092 (4.2)	419 (5.0)	1,082 (4.9)	33 (7.6)
Index of Multiple Deprivation				
1	4,607 (17.6)	1,533 (18.3)	3,812 (17.2)	92 (21.1)
2	4,755 (18.2)	1,703 (20.4)	4,172 (18.8)	88 (20.1)
3	5,147 (19.6)	1,613 (19.3)	4,296 (19.3)	80 (18.3)
4	5,744 (21.9)	1,690 (20.2)	4,776 (21.5)	96 (22.0)
5	5,912 (22.6)	1,821 (21.8)	5,143 (23.1)	81 (18.5)
Missing	33 (0.1)	8 (0.1)	27 (0.1)	0 (0.0)
Smoking	19,458 (74.3)	6,191 (74.0)	16,420 (73.9)	340 (77.8)
BMI, kg/m^2, mean(SD)	30.9 (6.7)	31.4 (7.0)	30.6 (6.6)	33.7 (7.7)
<25	4,284 (16.4)	1,310 (15.7)	3,958 (17.8)	46 (10.5)
25 to 29.9	7,782 (29.7)	2,407 (28.8)	6,930 (31.2)	98 (22.4)
30 to 34.9	6,752 (25.8)	2,278 (27.2)	5,694 (25.6)	112 (25.6)
35 to 39.9	3,471 (13.2)	1,250 (14.9)	2,822 (12.7)	96 (22.0)
40+	2,263 (8.6)	893 (10.7)	1,813 (8.2)	75 (17.2)
Missing	1,646 (6.3)	230 (2.7)	1,009 (4.5)	10 (2.3)
HbA1c, %, mean (SD)	9.7 (2.2)	9.7 (2.1)	9.7 (2.1)	10.1 (2.1)
<6.5	1,340 (5.1)	335 (4.0)	789 (3.5)	6 (1.4)
6.5 to 8	3,999 (15.3)	1,112 (13.3)	3,509 (15.8)	59 (13.5)
8+	18,325 (69.9)	6,414 (76.6)	16,600 (74.7)	363 (83.1)
Missing	2,534 (9.7)	507 (6.1)	1,328 (6.0)	9 (2.1)
eGFR, ml/min/1.73m^2 , mean (SD)	68.0 (21.3)	69.3 (20.5)	67.6 (20.8)	73.3 (17.9)
<60	4,813 (18.4)	1,528 (18.3)	4,254 (19.1)	65 (14.9)
≥60	10,640 (40.6)	4,315 (51.6)	9,639 (43.4)	310 (70.9)
Missing	10,745 (41.0)	2,525 (30.2)	8,333 (37.5)	62 (14.2)
SBP, mmHg, mean (SD)	133.4 (17.6)	132.7 (16.5)	133.9 (17.2)	130.2 (13.5)

DBP, mmHg, mean (SD)	75.8 (10.3)	76.3 (10.0)	76.4 (10.3)	74.4 (9.00)
Comorbidities				
Acute kidney injury	3,444 (13.1)	655 (7.8)	2,403 (10.8)	77 (17.6)
Alcohol-related disease	6,112 (23.3)	1,976 (23.6)	4,830 (21.7)	127 (29.1)
Atrial fibrillation	2,617 (10.0)	676 (8.1)	2,039 (9.2)	45 (10.3)
Cancer	4,299 (16.4)	1,143 (13.7)	3,237 (14.6)	46 (10.5)
Chronic kidney disease	6,359 (24.3)	1,999 (23.9)	5,170 (23.3)	84 (19.2)
COPD	3,990 (15.2)	1,151 (13.8)	3,032 (13.6)	71 (16.2)
Coronary artery disease	8,580 (32.8)	2,276 (27.2)	6,759 (30.4)	122 (27.9)
Coronary revascularization	2,209 (8.4)	578 (6.9)	1,642 (7.4)	30 (6.9)
Dialysis	255 (1.0)	S	166 (0.7)	S
Dyslipidemia	24,679 (94.2)	7,981 (95.4)	21,330 (96.0)	429 (98.2)
Hypertension	15,721 (60.0)	4,958 (59.2)	13,564 (61.0)	287 (65.7)
Hypoglycemia	2,778 (10.6)	739 (8.8)	2,332 (10.5)	82 (18.8)
Myocardial infarction	2,197 (8.4)	421 (5.0)	1,249 (5.6)	22 (5.0)
Neuropathy	1,533 (5.9)	487 (5.8)	1,428 (6.4)	31 (7.1)
Peripheral vascular disease	3,473 (13.3)	899 (10.7)	2,986 (13.4)	50 (11.4)
Retinopathy	11,429 (43.6)	3,851 (46.0)	9,476 (42.6)	253 (57.9)
Stroke	1,199 (4.6)	253 (3.0)	921 (4.1)	18 (4.1)
Previous use of other antidiabetic drugs				
Metformin	19,088 (72.9)	6,603 (78.9)	17,285 (77.8)	369 (84.4)
Sulfonylureas	17,913 (68.4)	5,793 (69.2)	15,943 (71.7)	271 (62.0)
TZD	11,610 (44.3)	4,253 (50.8)	10,659 (48.0)	359 (82.2)
DPP-4 inhibitors	6,381 (24.4)	1,955 (23.4)	4,871 (21.9)	174 (39.8)
GLP-1 receptor agonists	2,520 (9.6)	1,062 (12.7)	1,673 (7.5)	261 (59.7)
Alpha-glucosidase inhibitors	452 (1.7)	S	391 (1.8)	S
SGLT-2 inhibitors	1,283 (4.9)	234 (2.8)	925 (4.2)	125 (28.6)
Previous use of other drugs				
ACE inhibitors	13,169 (50.3)	4,304 (51.4)	11,358 (51.1)	229 (52.4)
Antiplatelets	10,720 (40.9)	3,611 (43.2)	10,019 (45.1)	133 (30.4)
ARB	7,791 (29.7)	2,536 (30.3)	6,701 (30.1)	139 (31.8)
Beta-blockers	8,030 (30.7)	2,328 (27.8)	6,328 (28.5)	113 (25.9)
Calcium-channel blockers	7,932 (30.3)	2,408 (28.8)	6,599 (29.7)	117 (26.8)
Diuretics	9,816 (37.5)	2,936 (35.1)	8,303 (37.4)	121 (27.7)
DOAC	467 (1.8)	90 (1.1)	289 (1.3)	23 (5.3)
NSAID	6,199 (23.7)	1,971 (23.6)	5,287 (23.8)	115 (26.3)
Statins	17,701 (67.6)	6,164 (73.7)	16,007 (72.0)	332 (76.0)

Abbreviations: NPH: neutral protamine Hagedorn, aSD: absolute standardized difference, SD: standard deviation. BMI: body mass index, HbA1c: glycated hemoglobin, eGFR: estimated glomerular filtration rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, COPD: chronic obstructive pulmonary disorder, TZD: thiazolidinediones, DPP-4: dipeptidyl peptidase-4, GLP-1: glucagon-like peptide-1, SGLT-

2: sodium-glucose co-transporter 2, ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blockers, DOAC: direct oral anticoagulants, NSAID: non-steroidal anti-inflammatory drugs

Smoking status and comorbidities were measured at any time prior to cohort entry. Medication use was measured in the year prior to cohort entry. The most recent measurement in the 5 years prior to cohort entry was used for HbA1c, eGFR, BMI, SBP and DBP. * Percentages represent proportion of the total cohort.

e-Table 3: Secondary analyses of risk of major adverse cardiovascular events (MACE) with the current use of long-acting insulin analogues and NPH among patients with type 2 diabetes in the UK, stratified by baseline age categories, sex, history of cardiovascular disease, and concomitant use of antidiabetic drugs at baseline.

Exposure	Events	Person-years	Crude IR* (95% CI)	Weighted HR† (95% CI)	Weighted and adjusted HR†‡§ (95% CI)
Age					
< 70					
Overall	1,361	65,747	20.7 (19.6 to 21.8)	-	-
NPH	661	26,380	25.1 (23.2 to 27.0)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin	700	39,366	17.8 (16.5 to 19.1)	0.71 (0.63 to 0.79)	0.85 (0.76 to 0.95)
≥70					
Overall	2,133	27,690	77.0 (73.8 to 80.4)	-	-
NPH	1,158	13,995	82.7 (78.1 to 87.7)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin	975	13,696	71.2 (66.9 to 75.8)	0.86 (0.79 to 0.94)	0.99 (0.91 to 1.08)
Sex					
Women					
Overall	1,356	40,445	33.5 (31.8 to 35.4)	-	-
NPH	709	18,303	38.7 (36.0 to 41.7)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin	647	22,142	29.2 (27.1 to 31.6)	0.77 (0.69 to 0.85)	0.99 (0.89 to 1.11)
Male					
Overall	2,138	52,991	40.3 (38.7 to 42.1)	-	-
NPH	1,110	22,071	50.3 (47.4 to 53.3)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin	1,028	30,920	33.2 (31.3 to 35.3)	0.67 (0.62 to 0.73)	0.91 (0.83 to 0.99)
History of CVD					
No history of CVD					
Overall	1,403	64,984	21.6 (20.4 to 22.7)	-	-
NPH	665	26,715	24.9 (23.1 to 26.9)	1.00 (Reference)	1.00 (Reference)

Long-acting insulin	738	38,269	19.3 (17.9 to 20.7)	0.78 (0.70 to 0.87)	1.01 (0.90 to 1.13)
History of CVD					
Overall	2,091	28,453	73.5 (70.4 to 76.7)	-	-
NPH	1,154	14,793	84.5 (79.7 to 89.5)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin	937	13,660	63.3 (59.4 to 67.5)	0.75 (0.69 to 0.82)	0.91 (0.83 to 0.99)
Concomitant use of antidiabetic drugs					
No use of antidiabetic drugs					
Overall	1,135	22,590	50.2 (47.4 to 53.3)	-	-
NPH	655	11,277	58.1 (53.8 to 62.7)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin analogs	480	11,314	42.4 (38.8 to 46.4)	0.74 (0.66 to 0.84)	0.95 (0.84 to 1.08)
Use of antidiabetic drugs					
Overall	2,359	70,846	33.3 (32.0 to 34.7)	-	-
NPH	1,164	29,098	40.0 (37.8 to 42.4)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin analogs	1,195	41,748	28.6 (27.0 to 30.3)	0.74 (0.68 to 0.81)	0.86 (0.79 to 0.94)

Abbreviations: HR: Hazard ratio; IR: incidence rate; CI: confidence interval

[*] Per 1000 person-years

[†] Marginal structural model weighted with standardized weights using inverse probability of treatment weights (IPTW) and inverse probability of censoring weights (IPCWs).

[‡] Age and duration of treated diabetes were modeled as restricted cubic splines with 5 knots.

[§] The model was adjusted for the following covariates at baseline: age, sex, ethnicity, year of cohort entry, index of multiple deprivation quintile, duration of treated diabetes, smoking status (ever/never smoker), history of alcohol-related disorders, coronary artery disease, myocardial infarction, stroke, chronic obstructive pulmonary disease, acute kidney injury, chronic kidney disease, neuropathy, retinopathy, peripheral vascular disease, atrial fibrillation. History of prescription drug use in the year prior to cohort entry included the following: metformin, sulfonylureas, thiazolidinediones, dipeptidyl-peptidase 4 inhibitors, glucagon-like peptide-1 receptor agonists, alpha-glucosidase inhibitors, sodium-glucose co-transporter 2 inhibitors, other antidiabetic drugs, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, diuretics, direct oral anticoagulants, antiplatelets, statins, non-

steroidal anti-inflammatory drugs. Clinical measurements were assessed in the year prior to cohort entry and included the following: body mass index, estimated glomerular filtration rate, glycated hemoglobin A1c, systolic blood pressure, diastolic blood pressure.
¶ Sum of events and person-time in molecule specific analyses do not add up to the totals for long-acting insulin analogues due to censoring upon combination use.

e-Table 4: Risk of major adverse cardiovascular events (MACE) with the current use of long-acting insulin analogues and NPH among patients with type 2 diabetes in the UK, varying from the grace period to 60 and 90 days.

Exposure	Events	Person-Years	Incidence Rate (95% CI) ‡	Crude HR (95% CI)	Weighted and adjusted HR†‡§ (95% CI) §
60-day grace period					
Overall	4,726	123,866	38.2	-	-
NPH	2,380	51,600	46.1 (44.3 to 48.0)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin analogs	2,346	72,267	32.5 (31.2 to 33.8)	0.72 (0.68 to 0.76)	0.93 (0.85 to 1.02)
90-day grace period					
Overall	5,632	142,850	39.4 (38.4 to 40.5)	-	-
NPH	2,766	58,446	47.3 (45.6 to 49.1)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin analogs	2,866	84,403	34.0 (32.7 to 35.2)	0.73 (0.69 to 0.77)	0.95 (0.86 to 1.05)

Abbreviations: HR: Hazard ratio; IR: incidence rate; CI: confidence interval

* Per 1000 person-years

† Marginal structural model weighted with standardized weights using inverse probability of treatment weights (IPTW) and inverse probability of censoring weights (IPCWs).

‡ Age and duration of treated diabetes were modeled as restricted cubic splines with 5 knots.

§ The model was adjusted for the following covariates at baseline: age, sex, ethnicity, year of cohort entry, index of multiple deprivation quintile, duration of treated diabetes, smoking status (ever/ never), history of alcohol-related disorders, coronary artery disease, myocardial infarction, stroke, chronic obstructive pulmonary disease, acute kidney injury, chronic kidney disease, neuropathy, retinopathy, peripheral vascular disease, atrial fibrillation. History of prescription drug use in the year prior to cohort entry included the following: metformin, sulfonylureas, thiazolidinediones, dipeptidyl-peptidase 4 inhibitors, glucagon-like peptide-1 receptor agonists, alpha-glucosidase inhibitors, sodium-glucose co-transporter 2 inhibitors, other antidiabetic drugs, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, diuretics, direct oral anticoagulants, antiplatelets, statins, non-

steroidal anti-inflammatory drugs. Clinical measurements were assessed in the year prior to cohort entry and included the following: body mass index, estimated glomerular filtration rate, glycated hemoglobin A1c, systolic blood pressure, diastolic blood pressure.
¶ Sum of events and person-time in molecule specific analyses do not add up to the totals for long-acting insulin analogues due to censoring upon combination use.

e-Table 5: Risk of major adverse cardiovascular events (MACE) with the current use of long-acting insulin analogues and NPH among patients with type 2 diabetes in the UK, excluding patients with a hospitalization for heart failure, stroke, or myocardial infarction in the 30 days prior to cohort entry.

Exposure	Events	Person-Years	Incidence Rate (95% CI) ‡	Crude HR (95% CI)	Adjusted HR[†‡§] (95% CI) [§]
Overall	3,141	91,323	34.4 (33.2 to 35.6)	-	-
NPH	1,583	38,768	40.8 (38.9 to 42.9)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin analogs	1,558	52,554	29.6 (28.2 to 31.2)	0.74 (0.69 to 0.79)	0.89 (0.82 to 0.96)

Abbreviations: HR: Hazard ratio; IR: incidence rate; CI: confidence interval

[*] Per 1000 person-years

[†] Marginal structural model weighted with standardized weights using inverse probability of treatment weights (IPTW) and inverse probability of censoring weights (IPCWs).

[‡] Age and duration of treated diabetes were modeled as restricted cubic splines with 5 knots.

[§] The model was adjusted for the following covariates at baseline: age, sex, ethnicity, year of cohort entry, index of multiple deprivation quintile, duration of treated diabetes, smoking status (ever/ never smokers), history of alcohol-related disorders, coronary artery disease, myocardial infarction, stroke, chronic obstructive pulmonary disease, acute kidney injury, chronic kidney disease, neuropathy, retinopathy, peripheral vascular disease, atrial fibrillation. History of prescription drug use in the year prior to cohort entry included the following: metformin, sulfonylureas, thiazolidinediones, dipeptidyl-peptidase 4 inhibitors, glucagon-like peptide-1 receptor agonists, alpha-glucosidase inhibitors, sodium-glucose co-transporter 2 inhibitors, other antidiabetic drugs, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, diuretics, direct oral anticoagulants, antiplatelets, statins, non-steroidal anti-inflammatory drugs. Clinical measurements were assessed in the year prior to cohort entry and included the following: body mass index, estimated glomerular filtration rate, glycated hemoglobin A1c, systolic blood pressure, diastolic blood pressure.

[¶] Sum of events and person-time in molecule specific analyses do not add up to the totals for long-acting insulin analogues due to censoring upon combination use.

e-Table 6: Risk of major adverse cardiovascular events (MACE) with the current use of long-acting insulin analogues and NPH among patients with type 2 diabetes in the UK, assessed using a standard time-dependent Cox proportional hazards model with adjustment for baseline covariates.

Exposure	Events	Person-Years	Incidence Rate (95% CI) *	Crude HR (95% CI)	Adjusted HR (95% CI) †‡
Overall	11,735	274,664	42.7 (42.0 to 43.5)	-	-
NPH	2,974	65,404	45.5 (43.9 to 47.1)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin analogs	3,232	101,490	31.8 (30.7 to 33.0)	0.72 (0.68 to 0.75)	0.91 (0.84 to 0.98)
Glargine	2,344	71,622	32.5 (31.2 to 33.9)	0.73 (0.69 to 0.77)	0.90 (0.83 to 0.98)
Detemir	847	28,318	29.3 (27.4 to 31.4)	0.67 (0.62 to 0.73)	0.92 (0.82 to 1.02)
Degludec	36	1,550	19.2 (13.0 to 28.2)	0.59 (0.43 to 0.82)	0.90 (0.60 to 1.35)
No use or combination	5,529	107,926	51.2 (49.9 to 52.6)	1.21 (1.16 to 1.27)	1.40 (1.30 to 1.49)

Abbreviations: HR: Hazard ratio; IR: incidence rate; CI: confidence interval

* Per 1000 person-years

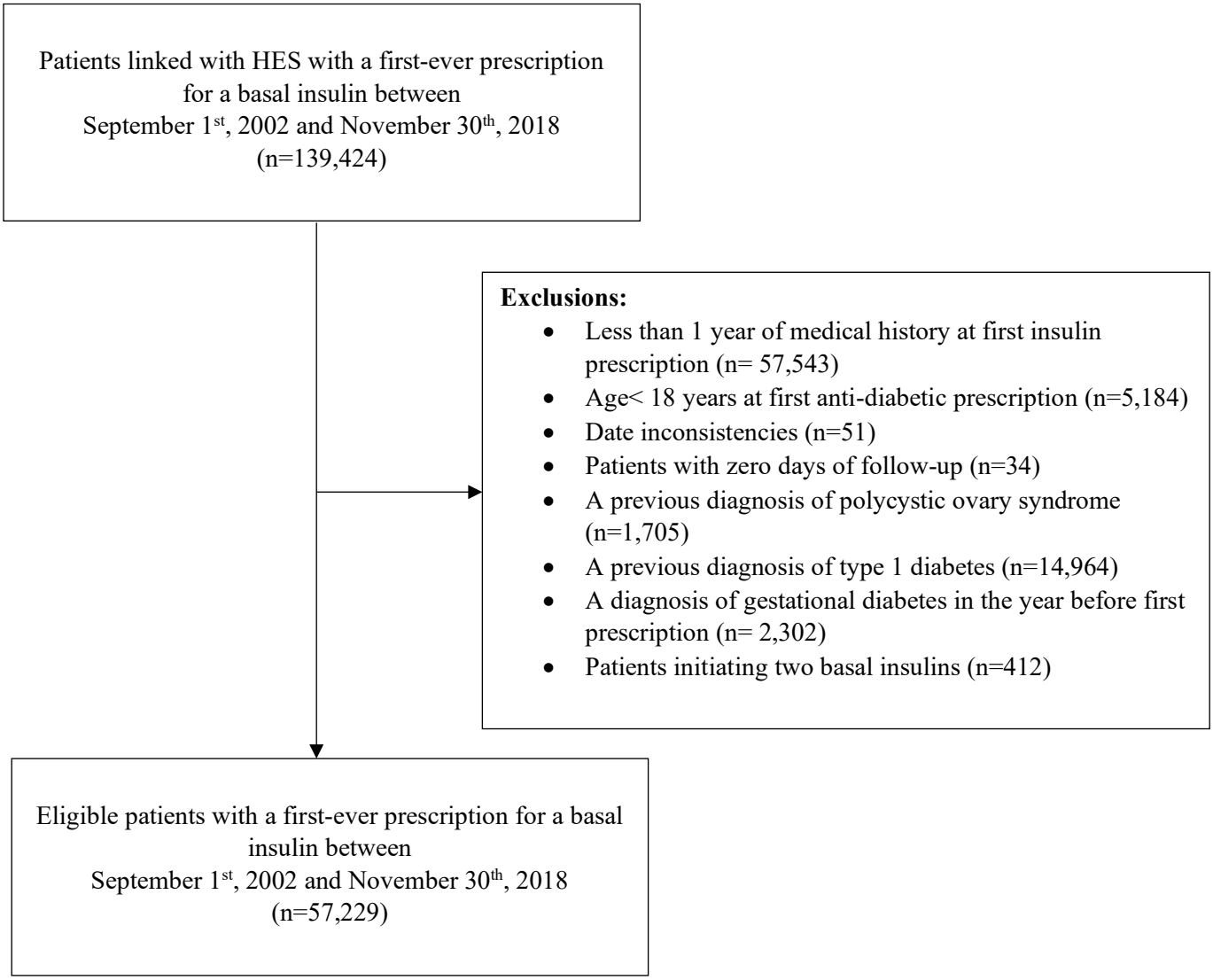
† Marginal structural model weighted with standardized weights using inverse probability of treatment weights (IPTW) and inverse probability of censoring weights (IPCWs).

‡ Age and duration of treated diabetes were modeled as restricted cubic splines with 5 knots.

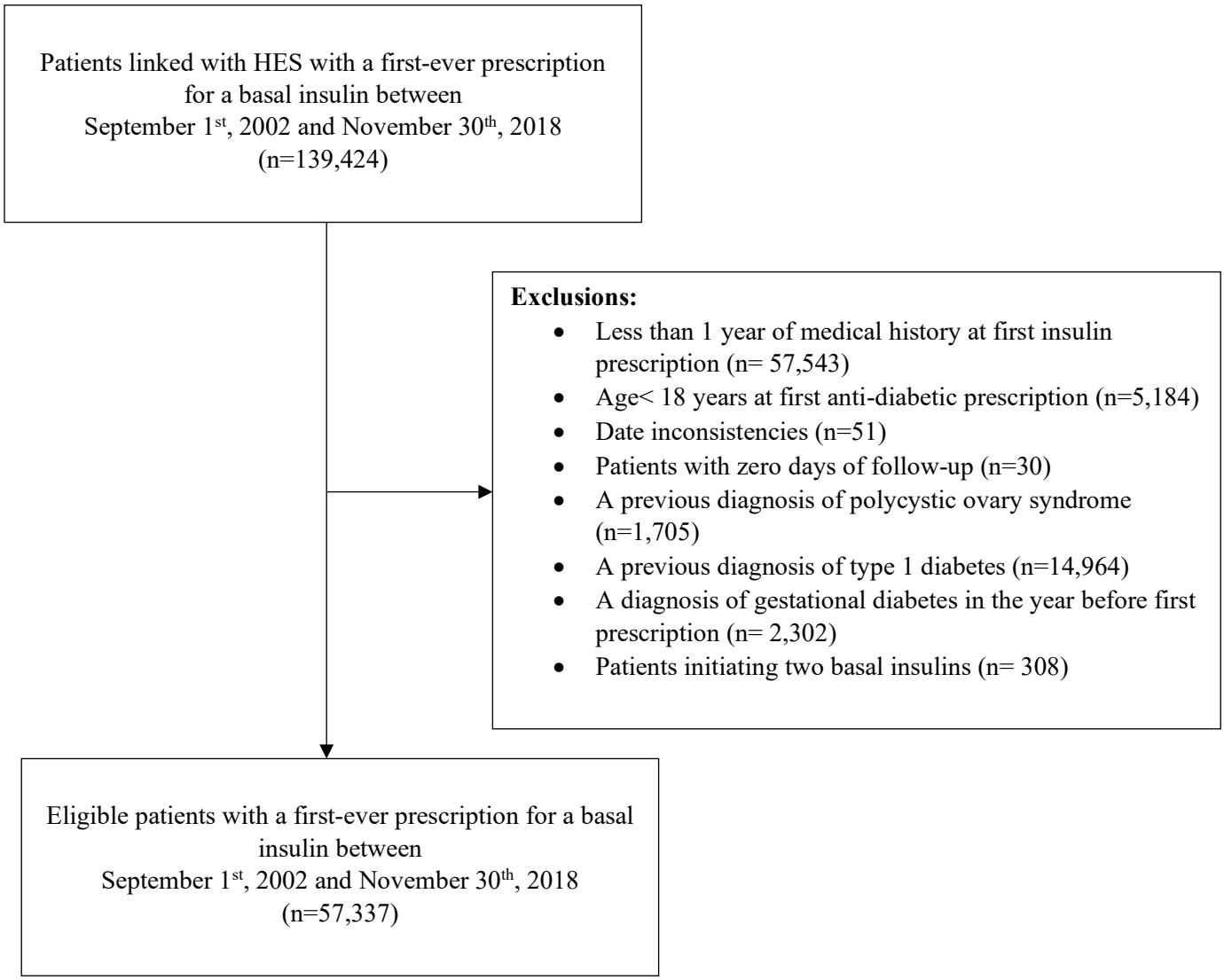
§ The model was adjusted for the following covariates at baseline: age, sex, ethnicity, year of cohort entry, index of multiple deprivation quintile, duration of treated diabetes, smoking status (ever/ never smokers), history of alcohol-related disorders, coronary artery disease, myocardial infarction, stroke, chronic obstructive pulmonary disease, acute kidney injury, chronic kidney disease, neuropathy, retinopathy, peripheral vascular disease, atrial fibrillation. History of prescription drug use in the year prior to cohort entry included the following: metformin, sulfonylureas, thiazolidinediones, dipeptidyl-peptidase 4 inhibitors, glucagon-like peptide-1 receptor agonists, alpha-glucosidase inhibitors, sodium-glucose co-transporter 2 inhibitors, other antidiabetic drugs, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, diuretics, direct oral anticoagulants, antiplatelets, statins, non-

steroidal anti-inflammatory drugs. Clinical measurements were assessed in the year prior to cohort entry and included the following: body mass index, estimated glomerular filtration rate, glycated hemoglobin A1c, systolic blood pressure, diastolic blood pressure.
¶ Sum of events and person-time in molecule specific analyses do not add up to the totals for long-acting insulin analogues due to censoring upon combination use.

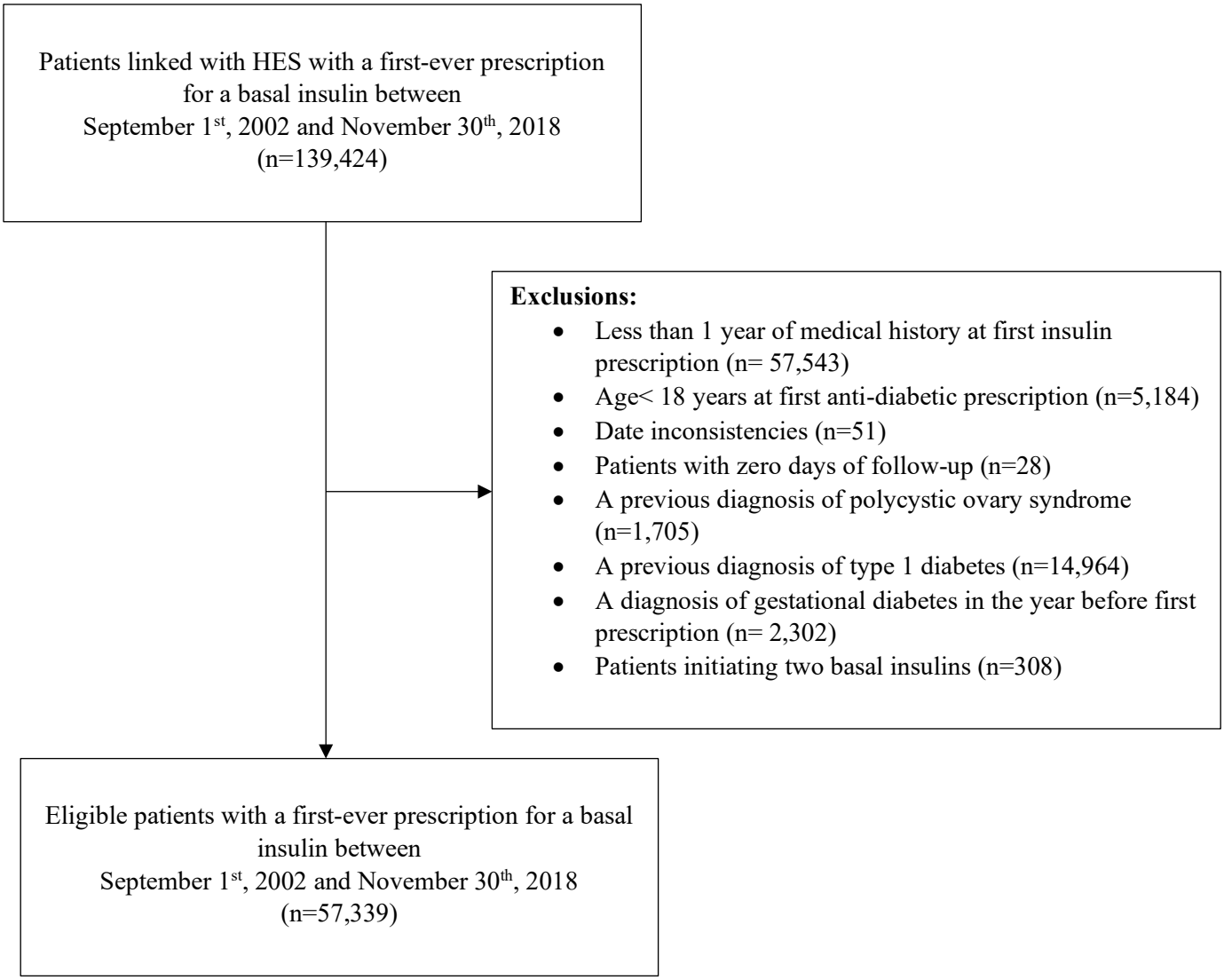
e-Figure 1: Study flow-chart for primary analysis on the association between current use of individual long-acting insulin analogs (glargine, detemir, degludec) and NPH and the risk of major adverse cardiovascular events (MACE)



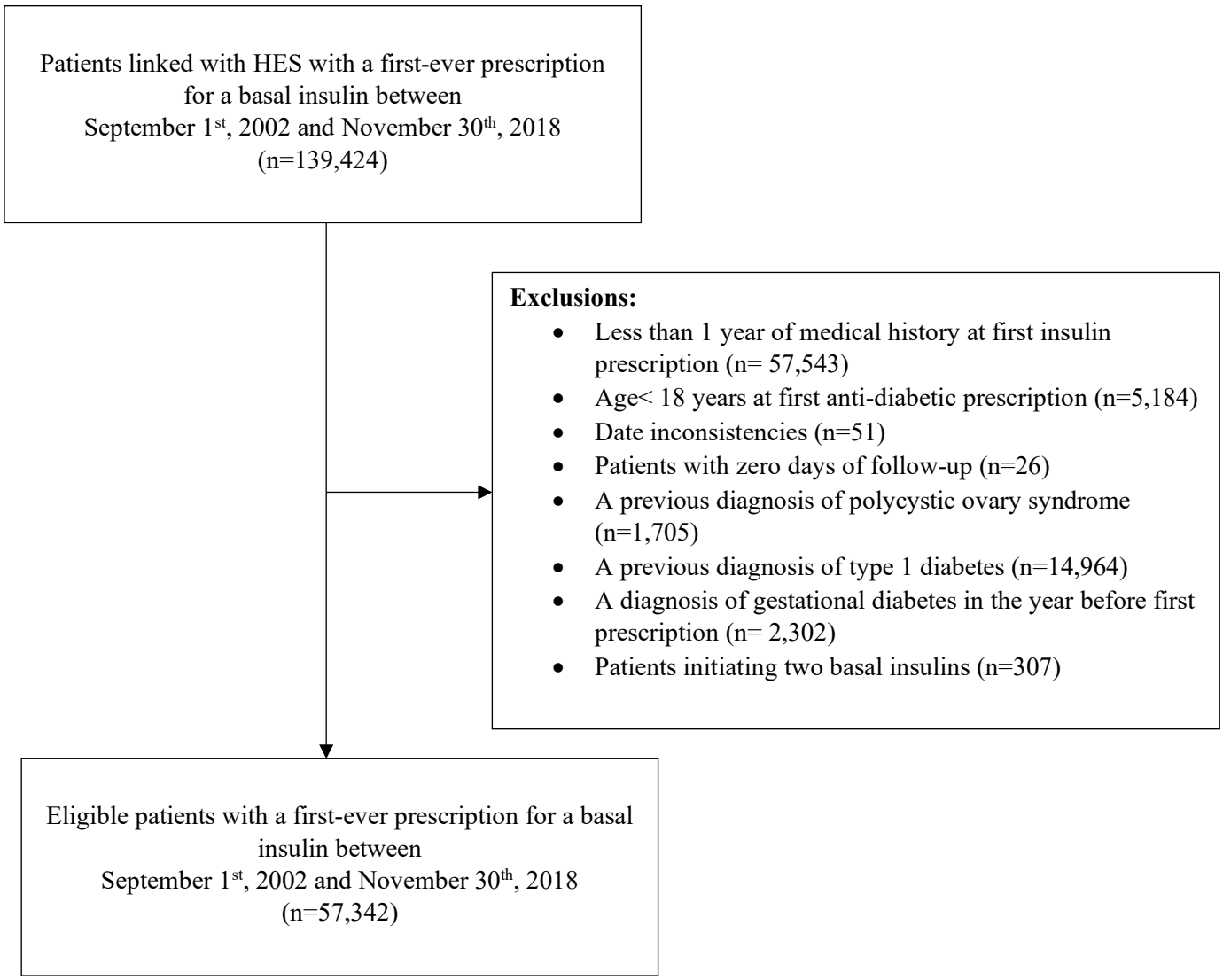
e-Figure 2: Flow chart for secondary analysis of the association between current use of long-acting insulin analogs and the risk of myocardial infarction (MI).



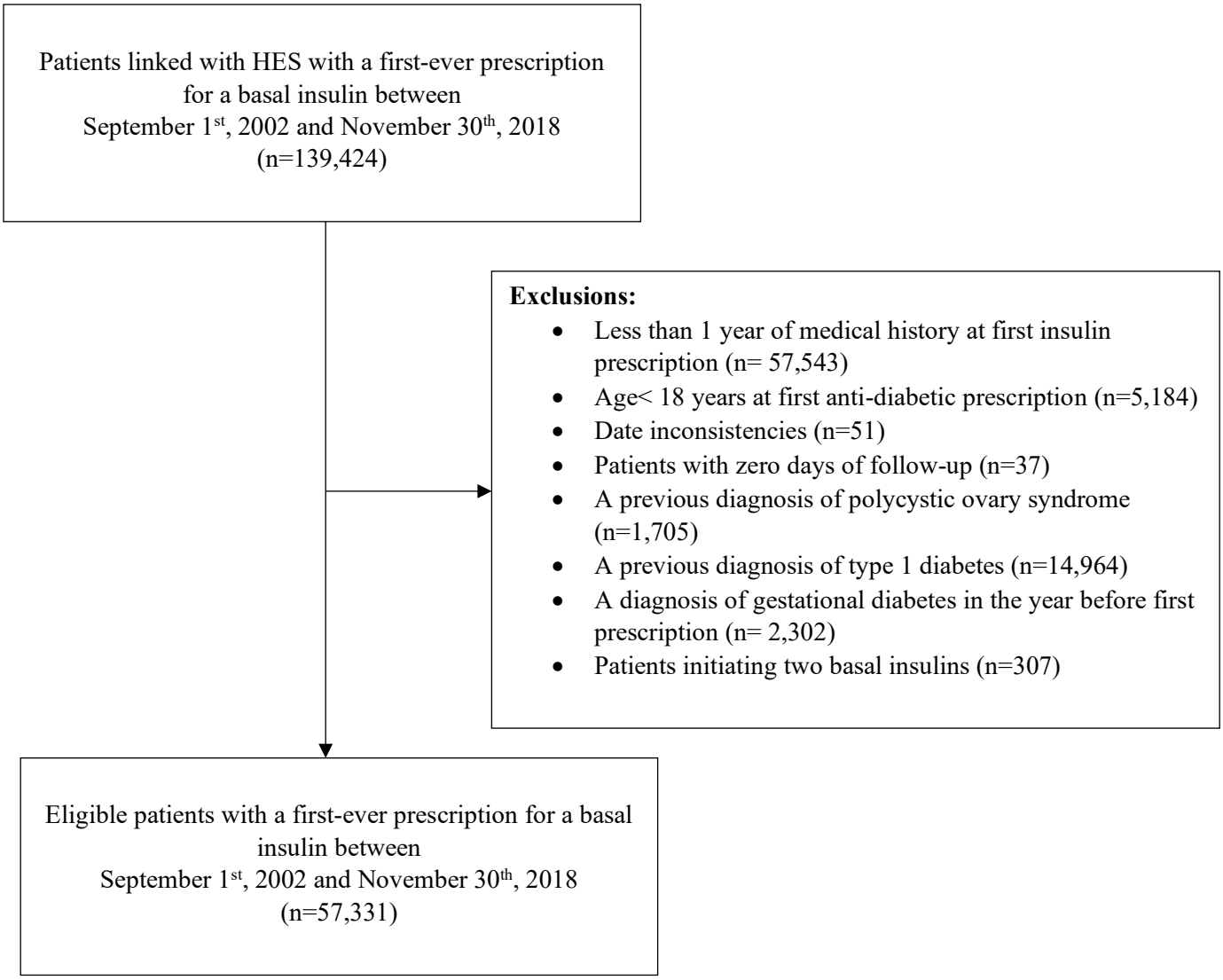
e-Figure 3: Flow chart for secondary analysis of the association between current use of long-acting insulin analogs and the risk of ischemic stroke.



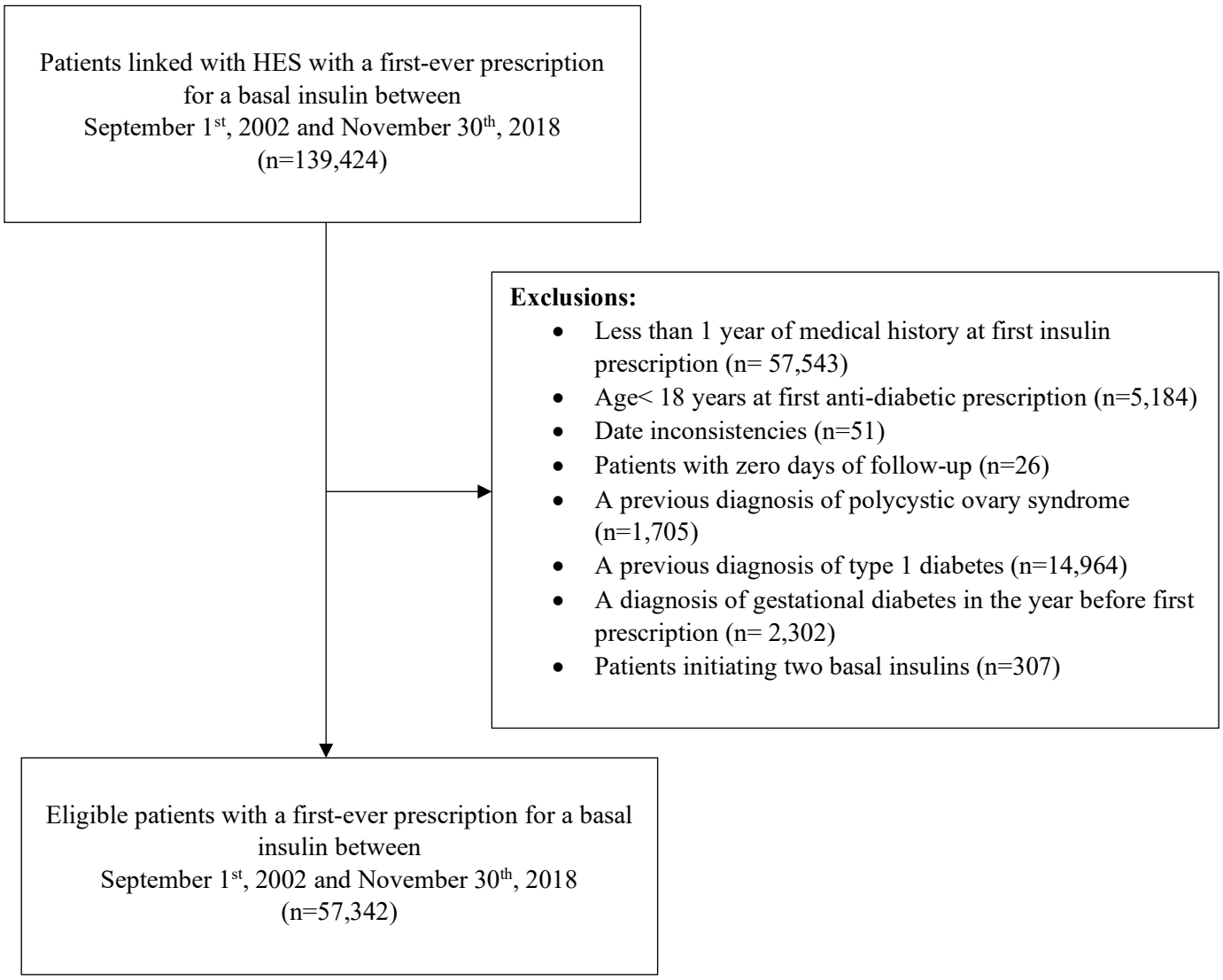
e-Figure 4: Flow chart for secondary analysis of the association between current use of long-acting insulin analogs and the risk of cardiovascular death.



e-Figure 5: Flow chart for secondary analysis of the association between current use of long-acting insulin analogs and the risk of hospitalization for heart failure.



e-Figure 6: Flow chart for secondary analysis of the association between current use of long-acting insulin analogs and the risk of all-cause mortality.



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