SUPPLEMENTARY DATA

Supplementary for the article: Lee AK et al. The Association of Severe Hypoglycemia with Incident Cardiovascular Events and Mortality in Adults with Type 2 Diabetes.

Supplementary Table S1. Visit 4 characteristics of ARIC participants included and excluded from the study population due to missing covariates.

	Study population n=1209 mean ± SD or %	**Excluded from study population n=292** mean ± SD or %	**p-value**
Age	63.6 ± 5.7	63.2 ± 5.68	0.28
Female	54.4	55.8	0.67
Black	33.7	51.0	<0.001
BMI	31.6 ± 5.9	31.9 ± 6.21	0.37
Diabetes medications			0.44
None	26.6	23.0	
Oral medication(s) only	44.7	46.4	
Any insulin	28.6	30.6	
Fructosamine			n/a
Middle tertile (296-351μmol/L)	33.1	n/a	
Highest tertile (≥352μmol/L)	33.0		
Diabetes duration ≥9 years	43.6	41.8	0.58
eGFR <60 mL/min/1.73 m^2	12.0	12.1	0.95
Albuminuria			0.02
ACR 30 - <300 mg/g	14.8	21.5	
ACR ≥300 mg/g	7.9	8.6	
Household income			0.001
<$12,000	19.4	32.6	
$12,000 – 23,999	27.0	23.2	
$24,000 – 49,999	32.0	27.4	
≥$50,000	21.7	16.8	
Disability	26.1	24.5	0.59
Systolic blood pressure, mmHg	132.3 ± 19.6	135.2 ± 23.1	0.03
Hypertension medication	69.6	70.2	0.85
LDL cholesterol, mg/dL	117.5 ± 35.7	117.7 ± 32.0	0.94
HDL cholesterol, mg/dL	44.5 ± 14.1	44.9 ± 13.3	0.64
Cholesterol-lowering medication	24.6	21.4	0.27
Smoking status			0.11
Current smoker	13.1	16.2	
Former smoker	47.0	40.2	
History of Coronary Heart Disease at Visit 4	18.0	12.3	0.02

Of those excluded from the study population, all were missing fructosamine, 3 were missing blood pressure, 15 were missing LDL cholesterol, 12 were missing HDL cholesterol, 12 were missing cholesterol medications, 1 was missing diabetes medications, 12 were missing eGFR, 36 were missing ACR, 31 were missing disability, and 26 were missing smoking status.

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Supplementary Table S2. Hypoglycemia Hazard Ratios and 95% Confidence Intervals for All-Cause and Cause-Specific Mortality, by subgroups (n=1209).

	All-cause Mortality			Cardiovascular Mortality			Cancer Mortality			Other Mortality		
	HR	95% CI	p-value*	HR	95% CI	p-value*	HR	95% CI	p-value*	HR	95% CI	p-value*
Age												
<65 years	1.72	(1.21, 2.45)	0.90	1.44	(0.81, 2.57)	0.56	3.02	(1.43, 6.38)	0.60	1.56	(0.86, 2.84)	0.69
≥65 years	1.77	(1.34, 2.33)		1.77	(1.15, 2.74)		2.32	(1.15, 4.67)		1.35	(0.85, 2.13)	
Sex												
Male	1.99	(1.47, 2.69)	0.20	1.73	(1.07, 2.80)	0.74	2.16	(1.07, 4.37)	0.52	2.14	(1.31, 3.50)	**0.02**
Female	1.51	(1.11, 2.06)		1.54	(0.94, 2.53)		2.97	(1.42, 6.21)		0.91	(0.53, 1.58)	
Race												
White	1.90	(1.44, 2.52)	0.26	1.91	(1.20, 3.03)	0.44	2.68	(1.42, 5.05)	0.72	1.53	(0.97, 2.43)	0.47
Black	1.49	(1.06, 2.09)		1.47	(0.89, 2.44)		2.23	(0.96, 5.15)		1.17	(0.65, 2.10)	
Duration of Diabetes												
<9 years	1.68	(1.18, 2.39)	0.83	1.43	(0.80, 2.58)	0.57	2.25	(1.11, 4.57)	0.66	1.46	(0.78, 2.73)	0.87
≥9 years	1.76	(1.33, 2.33)		1.76	(1.14, 2.71)		2.82	(1.33, 5.96)		1.37	(0.87, 2.15)	
Prevalent CHD												
No	1.67	(1.28, 2.17)	0.51	1.92	(1.25, 2.95)	0.31	2.36	(1.25, 4.44)	0.85	1.08	(0.69, 1.68)	**0.01**
Yes	1.95	(1.32, 2.88)		1.33	(0.73, 2.44)		2.62	(1.08, 6.35)		3.10	(1.59, 6.02)	
Cardiovascular Risk**												
Low risk	1.64	(1.17, 2.30)	0.66	1.40	(0.78, 2.53)	0.48	1.48	(0.61, 3.60)	0.10	1.71	(1.01, 2.89)	0.32
High risk	1.81	(1.36, 2.41)		1.81	(1.17, 2.79)		3.54	(1.84, 6.80)		1.19	(0.71, 1.98)	

*p-value for interaction by the listed categories. **Cardiovascular Risk defined by inclusion criteria for the ACCORD trial.
Hazard Ratios were from interaction terms in Model 3; the likelihood ratio test was used to generate the p-value for interaction.

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Supplementary Table S3. Hypoglycemia Hazard Ratios and 95% Confidence Intervals for Coronary Heart Disease, Stroke, Heart Failure, Atrial Fibrillation, and Peripheral Artery Disease, by subgroups.

	Coronary Heart Disease			**Stroke**			**Heart Failure**			**Atrial Fibrillation**		
	HR	95% CI	p-value*	HR	95% CI	p-value*	HR	95% CI	p-value*	HR	95% CI	p-value*
Age												
<65 years	2.33	(1.18, 4.57)	0.59	0.14	(0.02, 1.07)	**0.01**	1.53	(0.94, 2.49)	0.51	1.40	(0.75, 2.63)	0.26
≥65 years	1.83	(1.01, 3.32)		1.48	(0.70, 3.14)		1.24	(0.80, 1.91)		0.87	(0.50, 1.51)	
Sex												
Male	1.79	(0.91, 3.51)	0.62	0.75	(0.26, 2.20)	0.86	1.53	(0.94, 2.49)	0.23	1.58	(0.88, 2.83)	0.08
Female	2.23	(1.23, 4.02)		0.85	(0.35, 2.06)		1.24	(0.80, 1.91)		0.76	(0.42, 1.37)	
Race												
White	1.69	(0.86, 3.31)	0.40	0.82	(0.32, 2.12)	0.91	1.50	(0.96, 2.35)	0.60	0.79	(0.46, 1.39)	0.09
Black	2.45	(1.34, 2.50)		0.76	(0.29, 2.00)		1.27	(0.80, 2.01)		1.63	(0.86, 3.07)	
Duration of Diabetes												
<9 years	1.94	(0.87, 4.33)	0.90	0.46	(0.11, 1.94)	0.31	1.50	(0.83, 2.71)	0.67	0.84	(0.38, 1.84)	0.49
≥9 years	2.05	(1.20, 3.52)		1.02	(0.46, 2.26)		1.29	(0.87, 1.91)		1.16	(0.70, 1.91)	
Cardiovascular Risk**												
Low risk	1.60	(0.81, 3.19)	0.30	1.05	(0.40, 2.74)	0.48	1.24	(0.74, 2.06)	0.61	0.92	(0.47, 1.80)	0.57
High risk	2.54	(1.41, 4.59)		0.65	(0.25, 1.70)		1.46	(0.96, 2.21)		1.16	(0.69, 1.97)	

*p-value for interaction by the listed categories. **Cardiovascular Risk defined by inclusion criteria for the ACCORD trial.
Hazard Ratios were from interaction terms in Model 3; the likelihood ratio test was used to generate the p-value for interaction.

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Supplementary Table S3, continued

	Peripheral Artery Disease		
	HR	95% CI	p-value*
Age			
<65 years	2.37	(1.10, 5.14)	0.13
≥65 years	1.01	(0.43, 2.41)	
Sex			
Male	2.38	(1.08, 5.21)	0.14
Female	1.06	(0.46, 2.41)	
Race			
White	1.01	(.41, 2.52)	0.17
Black	2.16	(1.03, 4.56)	
Duration of Diabetes			
<9 years	1.11	(0.32, 3.81)	0.51
≥9 years	1.72	(0.89, 3.32)	
Cardiovascular Risk**			
Low risk	0.70	(0.16, 3.05)	0.19
High risk	1.84	(0.96, 3.55)	

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SUPPLEMENTARY DATA

Supplementary Table S4. Hazard Ratios (95% Confidence Intervals) for the Association of Severe Hypoglycemia with Incident Cardiovascular Events and Mortality, excluding individuals with a history of severe hypoglycemia at Visit 4 (n=14)

	events / n	Model 1* HR (95%CI)	Model 2* HR (95%CI)	Model 3* HR (95%CI)
Incident Cardiovascular Events				
Coronary Heart Disease	168/980	2.73 (1.70 - 4.39)	2.19 (1.34 - 3.59)	2.18 (1.32 - 3.60)
Stroke	117/1150	0.93 (0.42 - 2.03)	0.74 (0.33 - 1.65)	0.67 (0.30 - 1.51)
Heart Failure	292/1176	2.26 (1.62 - 3.16)	1.35 (0.95 - 1.91)	1.36 (0.95 - 1.94)
Atrial Fibrillation	250/1148	1.52 (0.98 - 2.34)	1.13 (0.72 - 1.77)	1.07 (0.68 - 1.68)
Peripheral Artery Disease	85/1115	3.14 (1.71 - 5.78)	1.80 (0.95 - 3.39)	1.60 (0.84 - 3.06)
Mortality				
All-Cause Mortality	574/1195	2.61 (2.09 - 3.25)	1.97 (1.56 - 2.49)	1.89 (1.50 - 2.39)
Cardiovascular Mortality**	212/1195	2.80 (1.97 - 3.99)	1.90 (1.31 - 2.77)	1.85 (1.27 - 2.68)
Cancer Mortality**	119/1195	2.52 (1.51 - 4.21)	2.74 (1.60 - 4.68)	2.74 (1.59 - 4.72)
Other Mortality**	214/1195	2.35 (1.63 - 3.41)	1.53 (1.04 - 2.26)	1.47 (1.00 - 2.17)

*Model 1 was adjusted for age, sex, and race-center. Model 2 additionally included diabetes medications, fructosamine tertiles, duration of diabetes, low eGFR, albuminuria, income, and any difficulty with ADLs. Model 3 additionally included systolic blood pressure, hypertension medication use, LDL, HDL, cholesterol-lowering medication use, and smoking status.
**29 individuals were missing cause of death and were censored at the time of death in the analyses of cause-specific death.

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SUPPLEMENTARY DATA

Supplementary Table S5. Hazard Ratios (95% Confidence Intervals) for the Association of Severe Hypoglycemia with Incident Cardiovascular Events and Mortality, using HbA1c measured 6 years prior instead of fructosamine to account for glycemic control.

	events / n	Model 1* HR (95%CI)	Model 2* HR (95%CI)	Model 3* HR (95%CI)
Incident Cardiovascular Events				
Coronary Heart Disease	166/942	2.73 (1.74 - 4.26)	2.23 (1.40 - 3.59)	2.00 (1.23 - 3.24)
Stroke	113/1105	1.19 (0.61 - 2.33)	0.98 (0.49 - 1.96)	0.89 (0.44 - 1.79)
Heart Failure	284/1131	2.27 (1.64 - 3.13)	1.29 (0.91 - 1.83)	1.26 (0.89 - 1.79)
Atrial Fibrillation	248/1103	1.55 (1.03 - 2.33)	1.14 (0.74 - 1.76)	1.03 (0.66 - 1.58)
Peripheral Artery Disease	86/1072	3.33 (1.90 - 5.83)	1.89 (1.04 - 3.41)	1.61 (0.88 – 2.97)
Mortality				
All-Cause Mortality	550/1149	2.67 (2.15 - 3.32)	1.93 (1.53 - 2.43)	1.75 (1.38 - 2.21)
Cardiovascular Mortality**	201/1149	2.98 (2.11 - 4.20)	1.87 (1.29 - 2.72)	1.71 (1.18 - 2.49)
Cancer Mortality**	113/1149	2.42 (1.44 - 4.04)	2.56 (1.48 - 4.42)	2.39 (1.36 - 4.18)
Other Mortality**	209/1149	2.41 (1.68 - 3.45)	1.60 (1.09 - 2.35)	1.47 (1.00 - 2.17)

*Model 1 was adjusted for age, sex, and race-center. Model 2 additionally included diabetes medications, HbA1c tertiles (<6.3%, 6.3-7.6%, ≥7.7%), duration of diabetes, low eGFR, albuminuria, income, and any difficulty with ADLs. Model 3 additionally included systolic blood pressure, hypertension medication use, LDL, HDL, cholesterol-lowering medication use, and smoking status.
**27 individuals were missing cause of death and were censored at the time of death in the analyses of cause-specific death.

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SUPPLEMENTARY DATA

Supplementary Table S6. Summary of Severe Hypoglycemia Incidence Rates in Observational Studies and Randomized Clinical Trials.

Reference (#)	Study Population	Definition of Severe Hypoglycemia	Severe Hypoglycemia Incidence Rate (PY = person-years)
Leese, 2003 Diabetes Care (33)	7678 participants with type 2 diabetes, mean age 66, mean duration 8 years in Tayside, Scotland	All hypoglycemia treated by emergency medical services	Type 2 on Sulphonylureas: 0.9 (0.6–1.3) per 100 diabetic PY Type 2 on insulin: 11.8 (9.5–14.1) per 100 diabetic PY
Huang 2014 JAMA Int Med (8)	72,310 adults aged 60+ with type 2 diabetes in Kaiser Permanente Diabetes Register (Northern California)	Hospitalization or emergency department use for hypoglycemia	Ranged from 0.3 per 100 diabetic PY for ages 60-69 and diabetes duration <10 years, to 2.0 per 100 diabetic PY for ages 80+ with diabetes duration >10 years
Lipska 2014 JAMA Int Med (34)	Adults on Medicare (mostly aged 65+)	Hospitalized hypoglycemia	0.6 per 100 diabetic PY
Lipksa 2016 Diabetes Care (35)	Adults in the OptumLabs Data Wearhouse (USA) who filled at least one diabetes medication	Hypoglycemia requiring emergency department use or hospitalization	1.3 per 100 diabetic PY
ACCORD Study Group 2008 NEJM (36)	10,251 participants with type 2 diabetes, mean age 62 years, median diabetes duration 10 years	Hypoglycemia requiring medical assistance (emergency department or hospitalization) Hypoglycemia requiring assistance (from another person, not medical professional)	Hypoglycemia requiring medical assistance: 1 per 100 diabetic PY in control arm, 3 per 100 diabetic PY in intensive arm. Hypoglycemia requiring any assistance (reported as proportion, not as incidence rate): 5% in control arm, 16% in intensive arm (over mean of 3.5 years follow-up in trial)
ADVANCE Collaborative Group, 2008 NEJM (37)	11,140 participants with type 2 diabetes, mean age 66 years, mean diabetes duration 8 years	Hypoglycemia requiring assistance from another person	0.3 per 100 diabetic PY in control arm, 0.7 per 100 diabetic PY in intensive arm
Duckworth 2009 NEJM (38)	(VADT) 1791 adults with type 2 diabetes, 98% male, mean age 60, mean diabetes duration 12 years	Hypoglycemia with impaired consciousness	3 per 100 diabetic PY in control arm, 9 per 100 diabetic PY in intensive arm

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ORIGIN Trial Investigators 2015 Diabetes Care (39)	11,081 adults with type 2 diabetes, mean age 64.	Hypoglycemia requiring assistance, with recovery after carbohydrates or documented plasma glucose <36mg/dL	0.9 per 100 diabetic PY
UKPDS Study Group 1998 Lancet (40)	3867 adults with newly diagnosed type 2 diabetes, median age 54	Hypoglycemia requiring third-party assistance	By treatment type, all per 100 diabetic PY: Insulin: 2.3 Chlorpropamide 0.4 Glibenclamide: 0.6 Diet: 0.1

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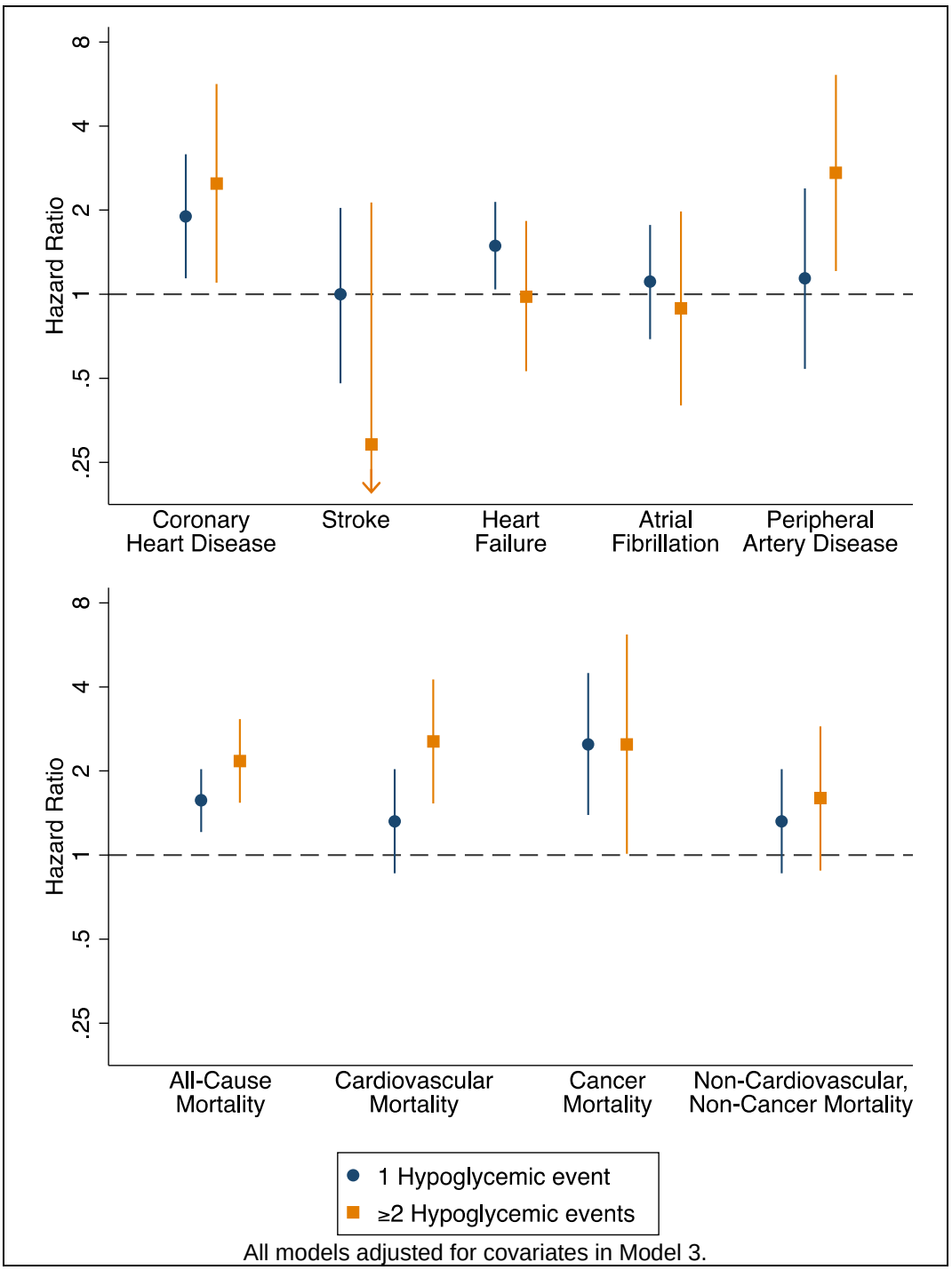
SUPPLEMENTARY DATA

Supplemental Figure S1. Hypoglycemia Hazard Ratios and 95% Confidence Intervals for Incident Cardiovascular Events and Mortality by Frequency of Hypoglycemia.



All models adjusted for covariates in Model 3.

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