Interplay of glycated hemoglobin and traditional risk factors for the risk of atherosclerotic cardiovascular disease and all-cause mortality in people without diabetes

Soroush Masrouri, Amirhossein Hasanpour, Navid Ebrahimi, and Farzad Hadaegh

Table S1. Multivariable-adjusted hazard ratios for atherosclerotic cardiovascular events and all-cause mortality associated with increasing risk factor burden and hemoglobin A1c

Table S2. Multivariable-adjusted hazard ratios for atherosclerotic cardiovascular events and all-cause mortality associated with increasing risk factor burden and hemoglobin A1c with exclusion of events in the first 3 years of follow-up

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Table S1. Multivariable-adjusted hazard ratios for atherosclerotic cardiovascular events and all-cause mortality associated with increasing cardiovascular risk factor burden (a) and hemoglobin A1c (b)

	ASCVD		All-cause mortality	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
a[*]				
0 RF	Reference	-	Reference	-
1 RF	1.70 (1.53-1.89)	<0.001	1.36 (1.26-1.46)	<0.001
2 RF	2.65 (2.38-2.95)	<0.001	1.85 (1.71-1.99)	<0.001
3 RF	3.64 (3.10-4.28)	<0.001	3.08 (2.75-3.46)	<0.001
b[†]				
HbA1c <5.0%	1.03 (0.91-1.17)	0.63	1.17 (1.07-1.28)	<0.001
HbA1c 5.0-5.4%	Reference	-	Reference	-
HbA1c 5.5-5.9%	1.17 (1.09-1.26)	<0.001	1.14 (1.07-1.20)	<0.001
HbA1c 6.0-6.4%	1.59 (1.42-1.78)	<0.001	1.35 (1.24-1.47)	<0.001

[*] Adjusted for age, sex, race, body mass index, and hemoglobin A1c category.

[†] Adjusted for age, sex, race, body mass index, and cardiovascular risk factor burden.

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Table S2. Multivariable-adjusted hazard ratios for atherosclerotic cardiovascular events and all-cause mortality associated with increasing cardiovascular risk factor burden (a) and hemoglobin A1c (b) with exclusion of events in the first 3 years of follow-up

	ASCVD		All-cause mortality	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
a[*]				
0 RF	Reference	-	Reference	-
1 RF	1.71 (1.54-1.91)	<0.001	1.38 (1.28-1.48)	<0.001
2 RF	2.72 (2.42-3.04)	<0.001	2.00 (1.85-2.16)	<0.001
3 RF	3.79 (3.18-4.51)	<0.001	3.43 (3.05-3.87)	<0.001
b[†]				
HbA1c <5.0%	0.94 (0.83-1.08)	0.38	1.12 (1.02-1.23)	0.02
HbA1c 5.0-5.4%	Reference	-	Reference	-
HbA1c 5.5-5.9%	1.19 (1.10-1.29)	<0.001	1.15 (1.09-1.22)	<0.001
HbA1c 6.0-6.4%	1.62 (1.43-1.83)	<0.001	1.38 (1.26-1.50)	<0.001

[*] Adjusted for age, sex, race, body mass index, and hemoglobin A1c category.

[†] Adjusted for age, sex, race, body mass index, and cardiovascular risk factor burden.

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Table S3. Multivariable-adjusted[*] hazard ratios for atherosclerotic cardiovascular events and all-cause mortality associated with increasing hemoglobin A1c according to cardiovascular risk factor strata with exclusion of events in the first 3 years of follow-up

	0 RF		1 RF		2 RF		3 RF	
	Case (%)	**HR (95% CI)**	**Case (%)**	**HR (95% CI)**	**Case (%)**	**HR (95% CI)**	**Case (%)**	**HR (95% CI)**
ASCVD								
HbA1c <5.0%	57 (6.6)	1.12 (0.84-1.51)	98 (10.6)	0.81 (0.65-0.99)	95 (21.1)	1.00 (0.80-1.25)	12 (28.6)	1.73 (0.91-3.30)
HbA1c 5.0-5.4%	213 (7.4)	Reference	583 (14.7)	Reference	473 (22.0)	Reference	44 (22.8)	Reference
HbA1c 5.5-5.9%	144 (9.6)	1.25 (1.01-1.56)	482 (16.5)	1.23 (1.08-1.40)	500 (23.4)	1.13 (0.99-1.28)	90 (28.4)	1.34 (0.93-1.92)
HbA1c 6.0-6.4%	27 (12.7)	1.76 (1.16-2.66)	133 (20.6)	1.60 (1.31-1.95)	175 (28.0)	1.51 (1.26-1.80)	43 (37.1)	2.24 (1.45-3.47)
All-cause mortality								
HbA1c <5.0%	128 (14.8)	1.26 (1.03-1.53)	219 (23.6)	1.06 (0.92-1.22)	189 (41.3)	1.14 (0.97-1.33)	21 (50.0)	1.42 (0.88-2.29)
HbA1c 5.0-5.4%	464 (16.2)	Reference	1,118 (28.2)	Reference	872 (39.9)	Reference	98 (48.8)	Reference
HbA1c 5.5-5.9%	322 (21.5)	1.14 (0.98-1.32)	983 (33.6)	1.16 (1.07-1.27)	957 (44.2)	1.11 (1.01-1.22)	201 (61.5)	1.29 (1.01-1.64)
HbA1c 6.0-6.4%	73 (35.1)	1.68 (1.30-2.18)	271 (41.4)	1.29 (1.12-1.49)	327 (50.8)	1.29 (1.13-1.48)	80 (69.0)	1.82 (1.34-2.48)

[*] Adjusted for age, sex, race, and body mass index.

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Table S4. Multivariable-adjusted hazard ratios for atherosclerotic cardiovascular events associated with increasing cardiovascular risk factor burden (a) and hemoglobin A1c (b) accounting for competing risk of non-ASCVD mortality

	HR (95% CI)	*P* value
a[*]		
0 RF	Reference	-
1 RF	1.71 (1.54-1.90)	<0.001
2 RF	2.58 (2.32-2.88)	<0.001
3 RF	3.35 (2.84-3.95)	<0.001
b[†]		
HbA1c <5.0%	0.91 (0.81-1.04)	0.19
HbA1c 5.0-5.4%	Reference	-
HbA1c 5.5-5.9%	1.15 (1.06-1.24)	<0.001
HbA1c 6.0-6.4%	1.52 (1.36-1.71)	<0.001

[*] Adjusted for age, sex, race, body mass index, and hemoglobin A1c category.
[†] Adjusted for age, sex, race, body mass index, and cardiovascular risk factor burden.

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Table S5. Multivariable-adjusted[*] hazard ratios for atherosclerotic cardiovascular events associated with increasing hemoglobin A1c according to cardiovascular risk factor strata accounting for competing risk of non-ASCVD mortality

	0 RF	1 RF	2 RF	3 RF
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
HbA1c <5.0%	1.07 (0.81-1.41)	0.79 (0.65-0.97)	1.01 (0.82-1.22)	1.32 (0.75-2.33)
HbA1c 5.0-5.4%	Reference	Reference	Reference	Reference
HbA1c 5.5-5.9%	1.23 (0.99-1.52)	1.16 (1.03-1.31)	1.11 (0.99-1.25)	1.19 (0.87-1.65)
HbA1c 6.0-6.4%	1.53 (1.01-2.34)	1.54 (1.28-1.86)	1.46 (1.23-1.72)	1.78 (1.21-2.64)

[*] Adjusted for age, sex, race, and body mass index.

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Table S6. Multivariable-adjusted[*] hazard ratios for atherosclerotic cardiovascular events and all-cause mortality associated with hemoglobin A1c categories, as defined by U.S. as well as Canadian/U.K. guidelines

	ASCVD		All-cause mortality	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
a				
HbA1c <5.0%	1.01 (0.90-1.14)	0.85	1.15 (1.05-1.25)	0.002
HbA1c 5.0-5.6%	Reference	-	Reference	-
HbA1c 5.7-6.4%	1.35 (1.25-1.45)	<0.001	1.22 (1.16-1.29)	<0.001
b				
HbA1c <5.0%	0.96 (0.85-1.08)	0.52	1.10 (1.01-1.20)	0.02
HbA1c 5.0-5.9%	Reference	-	Reference	-
HbA1c 6.0-6.4%	1.46 (1.32-1.62)	<0.001	1.25 (1.16-1.36)	<0.001

[*] Adjusted for age, sex, race, body mass index, and cardiovascular risk factor burden.

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Table S7. Multivariable-adjusted[*] hazard ratios for atherosclerotic cardiovascular events and all-cause mortality associated with increasing hemoglobin A1c, as defined by U.S. as well as Canadian/U.K. guidelines according to risk factor strata

	0 RF	1 RF	2 RF	3 RF
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
a				
ASCVD				
HbA1c <5.0%	1.17 (0.88-1.55)	0.85 (0.69-1.03)	1.12 (0.92-1.36)	1.61 (0.93-2.81)
HbA1c 5.0-5.6%	Reference	Reference	Reference	Reference
HbA1c 5.7-6.4%	1.52 (1.21-1.91)	1.29 (1.14-1.46)	1.33 (1.19-1.49)	1.56 (1.19-2.06)
All-cause mortality				
HbA1c <5.0%	1.24 (1.03-1.50)	1.09 (0.95-1.25)	1.18 (1.01-1.37)	1.47 (0.96-2.27)
HbA1c 5.0-5.6%	Reference	Reference	Reference	Reference
HbA1c 5.7-6.4%	1.28 (1.09-1.49)	1.19 (1.09-1.30)	1.14 (1.04-1.25)	1.45 (1.18-1.77)
b				
ASCVD				
HbA1c <5.0%	1.11 (0.84-1.45)	0.82 (0.67-0.99)	1.06 (0.87-1.27)	1.47 (0.86-2.51)
HbA1c 5.0-5.9%	Reference	Reference	Reference	Reference
HbA1c 6.0-6.4%	1.51 (1.02-2.25)	1.45 (1.21-1.73)	1.42 (1.22-1.65)	1.76 (1.27-2.43)
All-cause mortality				
HbA1c <5.0%	1.21 (1.01-1.46)	1.05 (0.92-1.21)	1.14 (0.98-1.31)	1.34 (0.88-2.04)
HbA1c 5.0-5.9%	Reference	Reference	Reference	Reference
HbA1c 6.0-6.4%	1.57 (1.23-2.00)	1.15 (1.01-1.31)	1.21 (1.08-1.37)	1.54 (1.20-1.97)

[*] Adjusted for age, sex, race, and body mass index.

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Table S8. Multivariable-adjusted[*] hazard ratios for atherosclerotic cardiovascular events and all-cause mortality associated with increasing hemoglobin A1c

	ASCVD		All-cause mortality	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
HbA1c <5.0%	0.99 (0.88-1.12)	0.90	1.13 (1.03-1.23)	0.01
HbA1c 5.0-5.4%	Reference	-	Reference	-
HbA1c 5.5-5.9%	1.16 (1.08-1.26)	<0.001	1.14 (1.08-1.21)	<0.001
HbA1c 6.0-6.4%	1.56 (1.39-1.75)	<0.001	1.34 (1.24-1.48)	<0.001

[*] Adjusted for age, sex, race, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, lipid-lowering medication use, systolic blood pressure, diastolic blood pressure, antihypertensive medication use, smoking status, and fasting plasma glucose.

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Table S9. Multivariable-adjusted hazard ratios for atherosclerotic cardiovascular events and all-cause mortality associated with increasing cardiovascular risk factor burden (a) and hemoglobin A1c (b), further adjusting for education level and C-reactive protein (n = 19,703)

	ASCVD		All-cause mortality	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
a[*]				
0 RF	Reference	-	Reference	-
1 RF	1.65 (1.48-1.84)	<0.001	1.31 (1.21-1.41)	<0.001
2 RF	2.52 (2.26-2.81)	<0.001	1.73 (1.61-1.87)	<0.001
3 RF	3.16 (2.67-3.76)	<0.001	2.62 (2.32-2.96)	<0.001
b[†]				
HbA1c <5.0%	1.04 (0.92-1.18)	0.53	1.18 (1.08-1.30)	<0.001
HbA1c 5.0-5.4%	Reference	-	Reference	-
HbA1c 5.5-5.9%	1.15 (1.07-1.24)	<0.001	1.11 (1.05-1.18)	<0.001
HbA1c 6.0-6.4%	1.50 (1.33-1.69)	<0.001	1.25 (1.15-1.37)	<0.001

[*] Adjusted for age, sex, race, body mass index, hemoglobin A1c category, education level (less than high-school, high-school, some college), and C-reactive protein (natural log).

[†] Adjusted for age, sex, race, body mass index, cardiovascular risk factor burden, education level (less than high-school, high-school, some college), and C-reactive protein (natural log).

CRP levels were not normally distributed and were log-transformed prior to statistical analyses.

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Table S10. Multivariable-adjusted[*] hazard ratios for atherosclerotic cardiovascular events and all-cause mortality associated with increasing hemoglobin A1c, stratified by cardiovascular risk factor burden and further adjusting for education level and C-reactive protein (n = 19,703) *

	0 RF		1 RF		2 RF		3 RF	
	Case (%)	**HR (95% CI)**	**Case (%)**	**HR (95% CI)**	**Case (%)**	**HR (95% CI)**	**Case (%)**	**HR (95% CI)**
ASCVD								
HbA1c <5.0%	61 (7.0)	1.17 (0.88-1.56)	110 (11.9)	0.89 (0.73-1.10)	113 (24.6)	1.11 (0.91-1.37)	15 (34.1)	1.64 (0.91-2.94)
HbA1c 5.0-5.4%	220 (7.7)	Reference	622 (15.7)	Reference	525 (24.2)	Reference	55 (28.2)	Reference
HbA1c 5.5-5.9%	143 (9.86)	1.26 (1.01-1.56)	496 (17.6)	1.19 (1.06-1.35)	553 (25.9)	1.09 (0.97-1.23)	97 (31.1)	1.10 (0.78-1.53)
HbA1c 6.0-6.4%	25 (12.6)	1.59 (1.03-2.46)	137 (22.4)	1.52 (1.24-1.85)	189 (31.1)	1.45 (1.22-1.73)	36 (35.0)	1.54 (1.00-2.40)
All-cause mortality								
HbA1c <5.0%	131 (15.1)	1.24 (1.03-1.51)	228 (24.7)	1.15 (1.00-1.33)	198 (43.0)	1.22 (1.04-1.42)	23 (52.3)	1.47 (0.93-2.34)
HbA1c 5.0-5.4%	474 (16.7)	Reference	1,143 (28.9)	Reference	876 (40.4)	Reference	97 (49.7)	Reference
HbA1c 5.5-5.9%	317 (21.9)	1.12 (0.97-1.30)	951 (33.7)	1.11 (1.02-1.21)	959 (44.8)	1.09 (1.00-1.20)	188 (60.3)	1.22 (0.95-1.57)
HbA1c 6.0-6.4%	71 (35.7)	1.55 (1.20-2.02)	252 (41.2)	1.14 (0.98-1.31)	304 (50.0)	1.23 (1.06-1.41)	70 (68.0)	1.62 (1.17-2.23)

[*] Adjusted for age, sex, race, body mass index, education level (less than high-school, high-school, some college), and C-reactive protein (natural log).
CRP levels were not normally distributed and were log-transformed prior to statistical analyses.

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Table S11. Multivariable-adjusted hazard ratios for atherosclerotic cardiovascular events and all-cause mortality associated with increasing cardiovascular risk factor burden (a) and hemoglobin A1c (b), restricting follow-up to 10 years

	ASCVD		All-cause mortality	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
a[*]				
0 RF	Reference	-	Reference	-
1 RF	2.08 (1.73-2.50)	<0.001	1.53 (1.31-1.80)	<0.001
2 RF	3.70 (3.09-4.45)	<0.001	2.00 (1.70-2.35)	<0.001
3 RF	5.56 (4.37-7.07)	<0.001	3.51 (2.80-4.41)	<0.001
b[†]				
HbA1c <5.0%	1.17 (0.97-1.40)	0.099	1.35 (1.14-1.60)	0.001
HbA1c 5.0-5.4%	Reference	–	Reference	–
HbA1c 5.5-5.9%	1.20 (1.07-1.34)	0.002	1.14 (1.02-1.28)	0.024
HbA1c 6.0-6.4%	1.71 (1.46-2.01)	<0.001	1.34 (1.14-1.58)	<0.001

[*] Adjusted for age, sex, race, body mass index, and hemoglobin A1c category.

[†] Adjusted for age, sex, race, body mass index, and cardiovascular risk factor burden.

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Table S12. Multivariable-adjusted hazard ratios for atherosclerotic cardiovascular events and all-cause mortality associated with increasing cardiovascular risk factor burden (a) and hemoglobin A1c (b), with hypertension defined as blood pressure ≥140/90 mm Hg

	ASCVD		All-cause mortality	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
a[*]				
0 RF	Reference	-	Reference	-
1 RF	1.63 (1.48-1.79)	<0.001	1.36 (1.27-1.45)	<0.001
2 RF	2.48 (2.25-2.74)	<0.001	1.91 (1.78-2.05)	<0.001
3 RF	3.53 (2.99-4.17)	<0.001	3.22 (2.85-3.63)	<0.001
b[†]				
HbA1c <5.0%	1.03 (0.91-1.17)	0.631	1.17 (1.07-1.28)	0.001
HbA1c 5.0-5.4%	Reference	-	Reference	-
HbA1c 5.5-5.9%	1.18 (1.09-1.27)	<0.001	1.14 (1.08-1.21)	<0.001
HbA1c 6.0-6.4%	1.59 (1.42-1.78)	<0.001	1.34 (1.23-1.45)	<0.001

[*] Adjusted for age, sex, race, body mass index, and hemoglobin A1c category.
[†] Adjusted for age, sex, race, body mass index, and cardiovascular risk factor burden.

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Table S13. Multivariable-adjusted[*] hazard ratios for atherosclerotic cardiovascular events and all-cause mortality associated with increasing hemoglobin A1c, stratified by cardiovascular risk factor burden, with hypertension defined as blood pressure ≥140/90 mm Hg*

	0 RF		1 RF		2 RF		3 RF	
	Case (%)	**HR (95% CI)**	**Case (%)**	**HR (95% CI)**	**Case (%)**	**HR (95% CI)**	**Case (%)**	**HR (95% CI)**
ASCVD								
HbA1c <5.0%	81 (8.0)	1.24 (0.96-1.58)	115 (12.3)	0.80 (0.66-0.98)	97 (28.0)	1.27 (1.02-1.59)	12 (30.0)	1.49 (0.78-2.84)
HbA1c 5.0-5.4%	294 (8.6)	Reference	691 (17.4)	Reference	438 (24.8)	Reference	44 (27.7)	Reference
HbA1c 5.5-5.9%	213 (11.3)	1.30 (1.08-1.55)	566 (18.7)	1.14 (1.02-1.28)	512 (27.1)	1.16 (1.02-1.32)	85 (34.8)	1.31 (0.91-1.90)
HbA1c 6.0-6.4%	44 (15.0)	1.77 (1.27-2.46)	164 (24.1)	1.55 (1.29-1.85)	191 (32.9)	1.54 (1.29-1.83)	45 (41.3)	1.92 (1.25-2.96)
All-cause mortality								
HbA1c <5.0%	154 (15.3)	1.19 (1.00-1.43)	256 (27.5)	1.15 (1.01-1.32)	157 (45.4)	1.20 (1.01-1.42)	23 (57.5)	1.51 (0.95-2.42)
HbA1c 5.0-5.4%	623 (18.1)	Reference	1,198 (30.1)	Reference	765 (43.3)	Reference	84 (52.8)	Reference
HbA1c 5.5-5.9%	434 (23.1)	1.09 (0.96-1.23)	1,068 (35.3)	1.11 (1.02-1.21)	916 (48.5)	1.19 (1.08-1.31)	158 (64.8)	1.19 (0.91-1.56)
HbA1c 6.0-6.4%	106 (36.2)	1.52 (1.22-1.89)	290 (42.7)	1.23 (1.07-1.41)	318 (54.7)	1.35 (1.18-1.55)	77 (70.6)	1.58 (1.15-2.18)

[*] Adjusted for age, sex, race, and body mass index.

Interplay of glycated hemoglobin and traditional risk factors for the risk of atherosclerotic cardiovascular disease and all-cause mortality in people without diabetes

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Table S14. Multivariable-adjusted sub-hazard ratios for atherosclerotic cardiovascular events and all-cause mortality associated with increasing cardiovascular risk factor burden (a) and hemoglobin A1c (b) in the multiply imputed dataset

	ASCVD		All-cause mortality	
	sHR (95% CI)	***P* value**	**sHR (95% CI)**	***P* value**
a[*]				
0 RF	Reference	-	Reference	-
1 RF	1.71 (1.54-1.90)	<0.001	1.35 (1.26-1.45)	<0.001
2 RF	2.65 (2.38-2.94)	<0.001	1.83 (1.71-1.97)	<0.001
3 RF	3.62 (3.08-4.25)	<0.001	3.10 (2.75-3.48)	<0.001
b[†]				
HbA1c <5.0%	1.01 (0.88-1.14)	0.90	1.16 (1.06-1.26)	0.001
HbA1c 5.0-5.4%	Reference	-	Reference	-
HbA1c 5.5-5.9%	1.18 (1.09-1.28)	<0.001	1.13 (1.07-1.20)	<0.001
HbA1c 6.0-6.4%	1.58 (1.41-1.77)	<0.001	1.32 (1.22-1.44)	<0.001

[*] Adjusted for age, sex, race, body mass index, and hemoglobin A1c category.

[†] Adjusted for age, sex, race, body mass index, and cardiovascular risk factor burden.

sHR = sub-hazard ratio

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Table S15. Multivariable-adjusted[*] sub-hazard ratios for atherosclerotic cardiovascular events and all-cause mortality associated with increasing hemoglobin A1c, stratified by cardiovascular risk factor burden in the multiply imputed dataset*

	0 RF	1 RF	2 RF	3 RF
	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)
ASCVD				
HbA1c <5.0%	1.17 (0.87-1.54)	0.88 (0.73-1.07)	1.10 (0.90-1.33)	1.50 (0.84-2.65)
HbA1c 5.0-5.4%	Reference	Reference	Reference	Reference
HbA1c 5.5-5.9%	1.28 (1.04-1.56)	1.21 (1.08-1.36)	1.11 (0.98-1.24)	1.23 (0.90-1.70)
HbA1c 6.0-6.4%	1.69 (1.14-2.51)	1.56 (1.30-1.87)	1.46 (1.25-1.72)	2.04 (1.40-2.98)
All-cause mortality				
HbA1c <5.0%	1.28 (1.06-1.54)	1.11 (0.97-1.27)	1.20 (1.03-1.38)	1.40 (0.90-2.17)
HbA1c 5.0-5.4%	Reference	Reference	Reference	Reference
HbA1c 5.5-5.9%	1.13 (0.98-1.29)	1.14 (1.05-1.24)	1.11 (1.02-1.21)	1.26 (1.01-1.59)
HbA1c 6.0-6.4%	1.59 (1.23-2.03)	1.21 (1.06-1.39)	1.28 (1.12-1.44)	1.78 (1.34-2.36)

[*] Adjusted for age, sex, race, and body mass index.
sHR= sub-hazard ratio