

SUPPLEMENTARY DATA

Supplementary Table S1. Codes used in study

Disease	ICD-10 codes for diagnoses and surgical procedures
<i>Charlson index categories</i>	
Myocardial infarction	I21;I22;I23
Congestive heart failure	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	I70; I71; I72; I73; I74; I77
Cerebrovascular disease	I60-I69; G45; G46
Dementia	F00-F03; F05.1; G30
Chronic pulmonary disease	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease	M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86
Ulcer disease	K22.1; K25-K28
Mild liver disease	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0
Diabetes	E10.0, E10.1; E10.9; E11.0; E11.1; E11.9
Hemiplegia	G81; G82
Moderate to severe renal disease	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61
Diabetes with end organ damage	E10.2-E10.8; E11.2-E11.8
Any tumor	C00-C75
Leukemia	C91-C95
Lymphoma	C81-C85; C88; C90; C96
Moderate to severe liver disease	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Metastatic solid tumor	C76-C80
AIDS	B21-B24
<i>Diabetes complications</i>	
Diabetes with any neurological complication	E104, E114, E144, G590, G632
Diabetes with any eye complication	E103, E113, E143, H340-H342, H280, H334, H450, H360, H540, H541, H544, H25, H268, H269, H430, H431, H438C, H439, H334A, H330, H335, procedures: KCKC10, KCKC15, KCKD65
Diabetes with any renal complication	E102, E112, E142, I120, N083, N06, N17-N19, R809, BJFD2, or prior clinical biochemical indication of renal disease (2 days with estimated glomerular filtration rate (eGFR) ≤ 60 ml/min/1.73m2, and/or 2 days with urinary albumin above the cut-off for microalbuminuria).
<i>Diabetes with any microvascular complication</i>	
	E104, E114, E144, G590, G632, E103, E113, E143, H340-H342, H280, H334, H450, H360, H540, H541, H544, H25, H268, H269, H430, H431, H438C, H439, H334A, H330, H335, procedures: KCKC10, KCKC15, KCKD65, E102, E112, E142, I120, N083, N06, N17-N19, R809, BJFD2
<i>Diabetes with any macrovascular complication: any of:</i>	
Any vascular surgery	KFNA, KFNB, KFNC, KFND, KFNE, KFNF, KFNG, KFNH, KFNW, KFLF, KPAE+F+H+N+P+Q, KPAW99, KPAU74, KPBE+F+H+N+P+Q, KPBW, KPGH10, KPCE+F+H+N+P+Q, KPCW99, KPCW20, KPCU74+82+83+84, KPGE+F+H+N+P+Q, KPGW99, KPGW20, KPFE+F+H+N+P+Q+W, KPFE+H+N+P+Q+W, KPGH20+21+22+23+30+31+40+99, KPDU74+82+83+84,

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Ischemic heart disease diagnosis including angina pectoris or coronary surgery	KPEU74+82+83+84, KPFU74+82+83+84, KPGU74+83+84+99, KPGW, KPWG, KAAL10, KAAL11 I20-I25, T822A, T823, KFNA, KFNB, KFNC, KFND, KFNE, KFNF, KFNG, KFNH, KFNW, KFLF
Atherosclerotic cerebrovascular disease including haemorrhage or thrombolysis/thrombectomy	I61, I63-I66, I672, I678-I679, I691, I693-I698, KAAL10, KAAL11
Atherosclerotic peripheral vascular disease incl. peripheral vascular surgery or limb amputation	I702, I742-I745, I739A, I739B, I739C, E105, E115, KPBE+F+H+N+P+Q, KPBW, KPGH10, KPGE+F+H+N+P+Q, KPGW99, KPGW20, KPEE+F+H+N+P+Q+W, KPFE+H+N+P+Q+W, KPGH20+21+22+23+30+31+40+99, KPDU74+82+83+84, KPEU74+82+83+84, KPFU74+82+83+84, KNBQ, KNCQ, KNDQ, KNEQ, KNFQ, KNGQ, KNHQ
Unspecific atherosclerotic disease, atherosclerotic renal or intestinal disease	I700, I708, I709, I740-I741, I748-I749, N280, I701, K550-K551, K558-559
<i>Other conditions</i>	
Hospital-diagnosed obesity	E65-E68
Alcoholism-related disorders	G312, G621, G721, I 426, K292, K860, K70, R780, T51, Z714, Z721

Drug	ATC-code
Any glucose-lowering drugs	A10A, A10B
Insulin	A10A
Biguanides (metformin)	A10BA, A10BD02, A10BD03, A10BD05, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13, A10BD14, A10BD15
Sulfonylureas	A10BB, A10BD04, A10BD02, A10BD06, A10BD01, A10BC01
Other non-insulin drugs:	
Meglitinides	A10BX02, A10BX03, A10BX08
Alpha-glucosidase-inhibitors	A10BF
Thiazolidinediones (glitazones)	A10BG, A10BD03, A10BD04, A10BD05, A10BD06, A10BD09, A10BD12
DPP4-inhibitors	A10BH, A10BD07, A10BD08, A10BD09, A10BD10, A10BD11, A10BD12, A10BD13
GLP-1 analogues	A10BX04, A10BX07, A10BX10
SGLT-2 inhibitors	A10BX09, A10BX11, A10BX12; A10BD15
Anti-platelet drugs	B01AC06, N02BA01, B01AC30, B01AC07, B01AC22, B01AC04, B01AC24
Statins	C10AA, C10BA C10BX
Antihypertensive treatment	C02, C03A, C03B, C03D, C03E, C07, C08, C09A, C09B, C09C, C09D, C09X
Psychiatric medications	N05BA, N06A, N05A, N05CD, N05CF

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Supplementary Table S2. Crude and adjusted hazard ratios (HRs) for the association between early HbA1c (%) level achieved 6 months after metformin initiation and subsequent cardiovascular outcomes and death

	Crude HR (95% CI)	Adjusted HR (95% CI)
<i>Combined event</i>		
<6.5%	1.0 (ref)	1.0 (ref)
6.5-6.9%	1.22 (1.11-1.35)	1.18 (1.07-1.30)
7.0-7.4%	1.26 (1.12 -1.42)	1.23 (1.09 -1.40)
7.5-7.9%	1.24 (1.06-1.44)	1.34 (1.14-1.57)
≥8%	1.41 (1.23-1.61)	1.59 (1.37-1.84)
<i>Myocardial infarction</i>		
<6.5%	1.0 (ref)	1.0 (ref)
6.5-6.9%	1.35 (1.07-1.70)	1.30 (1.02-1.64)
7.0-7.4%	1.24 (0.93 -1.65)	1.19 (0.88 -1.61)
7.5-7.9%	1.40 (0.98-1.97)	1.43 (0.98-2.08)
≥8%	1.33 (0.96-1.86)	1.47 (1.03-2.12)
<i>Stroke</i>		
<6.5%	1.0 (ref)	1.0 (ref)
6.5-6.9%	1.10 (0.89-1.34)	1.04 (0.84-1.28)
7.0-7.4%	1.19 (0.93 -1.51)	1.13 (0.87 -1.45)
7.5-7.9%	1.39 (1.03-1.86)	1.44 (1.05-1.95)
≥8%	1.27 (0.96-1.69)	1.43 (1.05-1.95)
<i>Death</i>		
<6.5%	1.0 (ref)	1.0 (ref)
6.5-6.9%	1.20 (1.07-1.35)	1.18 (1.05-1.33)
7.0-7.4%	1.25 (1.10 -1.44)	1.25 (1.08 -1.44)
7.5-7.9%	1.17 (0.98-1.40)	1.27 (1.05-1.53)
≥8%	1.41 (1.21-1.65)	1.61 (1.36-1.90)

*adjusted by age, gender, calendar year of follow-up start, macrovascular complications, microvascular complications, obesity, alcoholism, antiplatelet drugs, statins, antihypertensives,

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psychiatric medication, baseline HbA1c, reached cholesterol target, and other glucose-lowering therapy

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Supplementary Table S3. Crude and adjusted hazard ratios (HR) for the association between absolute change in HbA1c (delta, %) from baseline to 6 months after metformin initiation and subsequent cardiovascular outcomes and death

	Crude HR (95% CI)	Adjusted HR (95% CI)
<i>Combined event</i>		
Delta -4%	0.87 (0.76-0.99)	0.80 (0.65-0.97)
Delta -3%	1.14 (0.98-1.32)	0.98 (0.80-1.20)
Delta -2%	1.12 (0.98-1.27)	0.92 (0.78-1.08)
Delta -1%	1.11 (1.01-1.23)	0.99 (0.89-1.10)
No change	1.0 (ref)	1.0 (ref)
Delta +1%	1.50 (1.17-1.92)	1.37 (1.07-1.76)
Delta ≥ +2%	1.83 (1.17-2.85)	1.92 (1.19-3.08)
<i>Myocardial infarction</i>		
Delta -4%	0.73 (0.52-1.01)	0.63 (0.38-1.03)
Delta -3%	1.35 (0.96-1.88)	1.07 (0.67-1.71)
Delta -2%	1.10 (0.81-1.49)	0.91 (0.62-1.35)
Delta -1%	1.06 (0.84-1.35)	0.96 (0.75-1.24)
No change	1.0 (ref)	1.0 (ref)
Delta +1%	0.96 (0.47-1.96)	0.93 (0.45-1.91)
Delta ≥ +2%	0.51 (0.07-3.62)	0.65 (0.09-4.72)
<i>Stroke</i>		
Delta -4%	0.79 (0.60-1.05)	0.81 (0.53-1.25)
Delta -3%	1.09 (0.79-1.49)	1.01 (0.66-1.55)
Delta -2%	1.17 (0.90-1.51)	1.02 (0.73-1.41)
Delta -1%	1.05 (0.85-1.28)	0.95 (0.76-1.19)
No change	1.0 (ref)	1.0 (ref)
Delta +1%	1.16 (0.66-2.04)	1.14 (0.64-2.01)
Delta ≥ +2%	1.87 (0.77-4.55)	2.33 (0.94-5.76)

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<i>Death</i>		
Delta -4%	0.95 (0.81-1.11)	0.86 (0.68-1.09)
Delta -3%	1.16 (0.97-1.39)	0.99 (0.78-1.25)
Delta -2%	1.13 (0.97-1.31)	0.92 (0.76-1.11)
Delta -1%	1.17 (1.04-1.31)	1.04 (0.91-1.18)
No change	1.0 (ref)	1.0 (ref)
Delta +1%	1.72 (1.31-2.27)	1.58 (1.19-2.09)
Delta \geq +2%	1.80 (1.06-3.06)	1.79 (1.00-3.21)

*adjusted by age, gender, calendar year of follow-up start, macrovascular complications, microvascular complications, obesity, alcoholism, antiplatelet drugs, statins, antihypertensives, psychiatric medication, baseline HbA1c, reached cholesterol target, and other glucose-lowering therapy

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Supplementary Table S4. Crude and adjusted hazard ratios (HRs) for the association between early HbA1c (%) level achieved 6 months after metformin initiation and subsequent combined outcome event (acute myocardial infarction, stroke, or death): Sensitivity analysis restricted to counting only events occurring at least 2 years after metformin start; and restricted to events occurring among patients with at least 5 years of follow-up, respectively.

	<i>HbA1c level achieved after 6 months</i>	Crude HR (95% CI)	Adjusted HR (95% CI)
Follow-up start 2 years after metformin start	<6.5%	1.0 (ref)	1.0 (ref)
	6.5-6.9%	1.18 (1.04-1.33)	1.15 (1.01-1.30)
	7.0-7.4%	1.20 (1.04 -1.39)	1.18 (1.02 -1.40)
	7.5-7.9%	1.17 (0.98-1.40)	1.25 (1.03-1.51)
	≥8%	1.28 (1.09-1.50)	1.43 (1.20-1.71)
Restricted to patients with at least 5 years of follow-up	<6.5%	1.0 (ref)	1.0 (ref)
	6.5-6.9%	1.00 (0.87-1.15)	0.99 (0.87-1.15)
	7.0-7.4%	1.14 (0.98 -1.33)	1.18 (1.01 -1.39)
	7.5-7.9%	1.07 (0.88-1.29)	1.15 (0.94-1.41)
	≥8%	1.23 (1.04-1.46)	1.39 (1.15-1.67)

*adjusted by age, gender, calendar year of follow-up start, macrovascular complications, microvascular complications, obesity, alcoholism, antiplatelet drugs, statins, antihypertensives, psychiatric medication, baseline HbA1c, reached cholesterol target, and other glucose-lowering therapy

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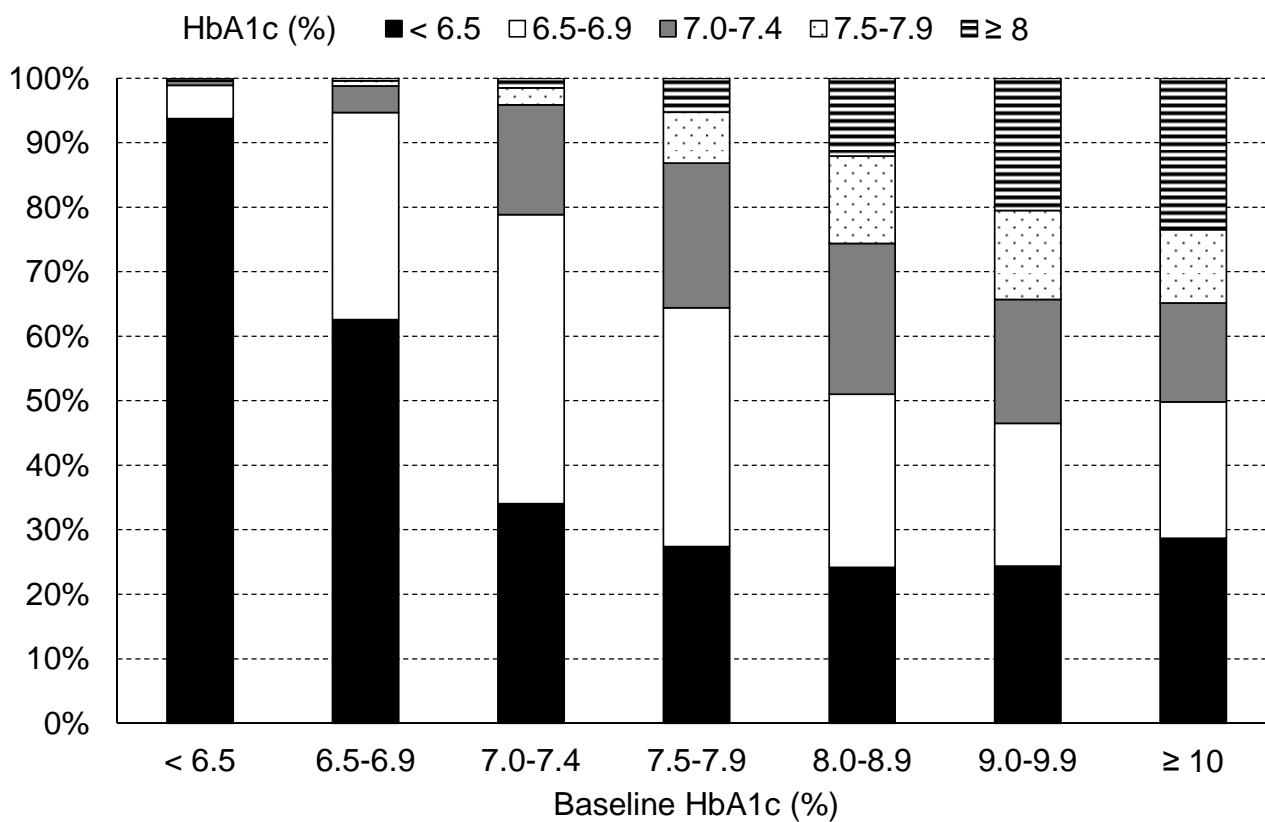
Supplementary Table S5. Crude and adjusted hazard ratios (HRs) for the association between absolute change in HbA1c (delta, %) from baseline to 6 months after metformin initiation and combined outcome event (acute myocardial infarction, stroke, or death): Sensitivity analysis restricted to counting only events occurring at least 2 years after metformin start; and restricted to events occurring among patients with at least 5 years of follow-up, respectively.

		Crude HR (95% CI)	Adjusted HR (95% CI)
<i>Absolute change</i>			
Follow-up start 2 years after metformin start	Delta -4%	0.90 (0.77-1.06)	0.85 (0.67-1.09)
	Delta -3%	1.18 (0.98-1.41)	1.04 (0.82-1.33)
	Delta -2%	1.13 (0.97-1.33)	0.97 (0.80-1.18)
	Delta -1%	1.10 (0.97-1.25)	0.99 (0.86-1.14)
	No change	1.0 (ref)	1.0 (ref)
	Delta +1%	1.21 (0.87-1.68)	1.15 (0.82-1.61)
	Delta \geq +2%	1.75 (0.99-3.10)	2.15 (1.17-3.94)
Restricted to patients with over 5 years of follow-up	Delta -4%	0.85 (0.71-1.01)	0.77 (0.60-1.00)
	Delta -3%	1.17 (0.96-1.42)	0.99 (0.77-1.29)
	Delta -2%	1.10 (0.93-1.31)	0.91 (0.74-1.12)
	Delta -1%	1.09 (0.94-1.26)	0.97 (0.83-1.14)
	No change	1.0 (ref)	1.0 (ref)
	Delta +1%	1.38 (0.99-1.92)	1.30 (0.93-1.82)
	Delta \geq +2%	1.44 (0.75-2.80)	1.08 (0.49-2.38)

*adjusted by age, gender, calendar year of follow-up start, macrovascular complications, microvascular complications, obesity, alcoholism, antiplatelet drugs, statins, antihypertensives, psychiatric medication, baseline HbA1c, reached cholesterol target, and other glucose-lowering therapy

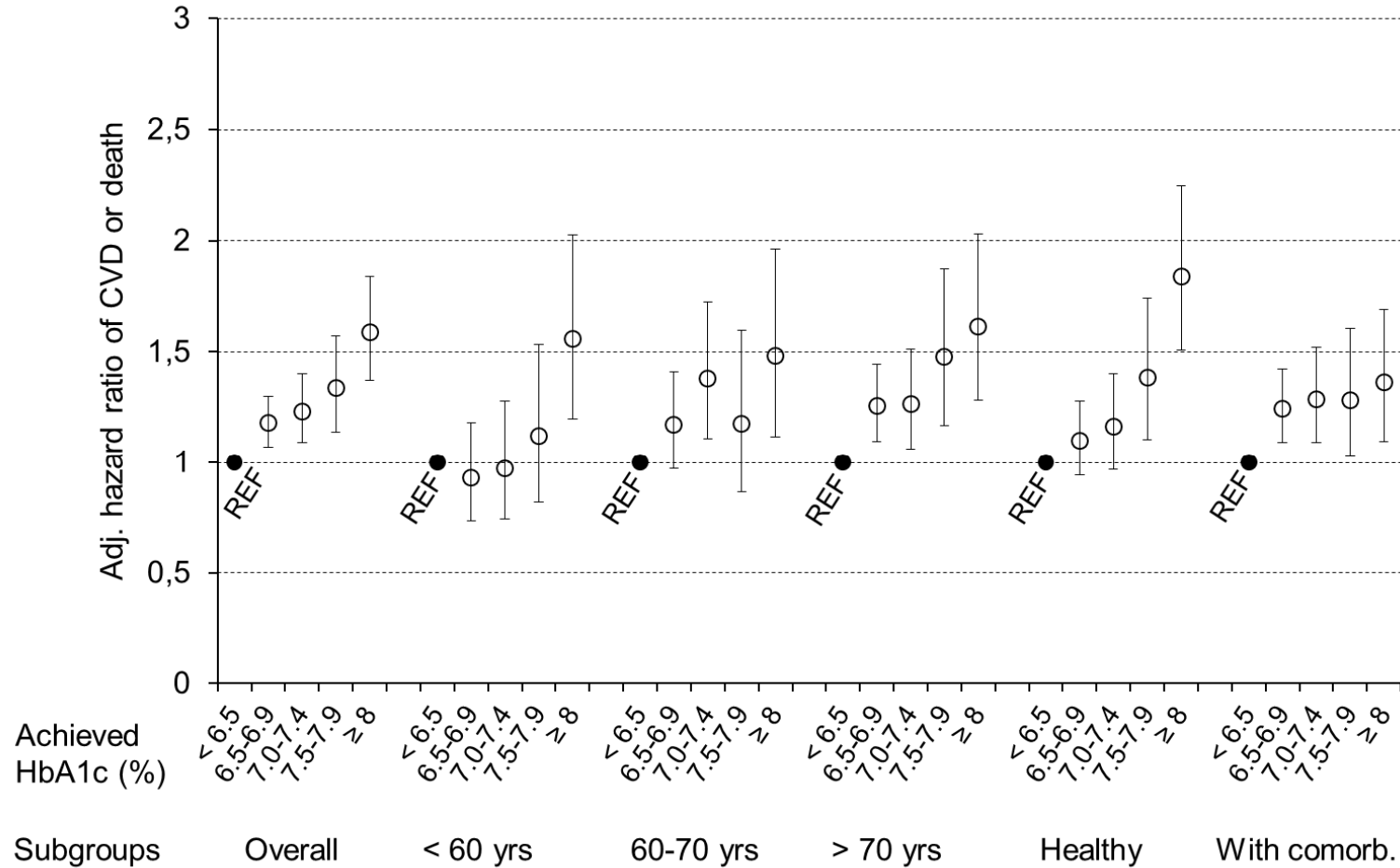
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Supplementary Figure S1. Achieved levels of HbA1c at 6 months after metformin initiation, stratified by baseline HbA1c before metformin initiation.



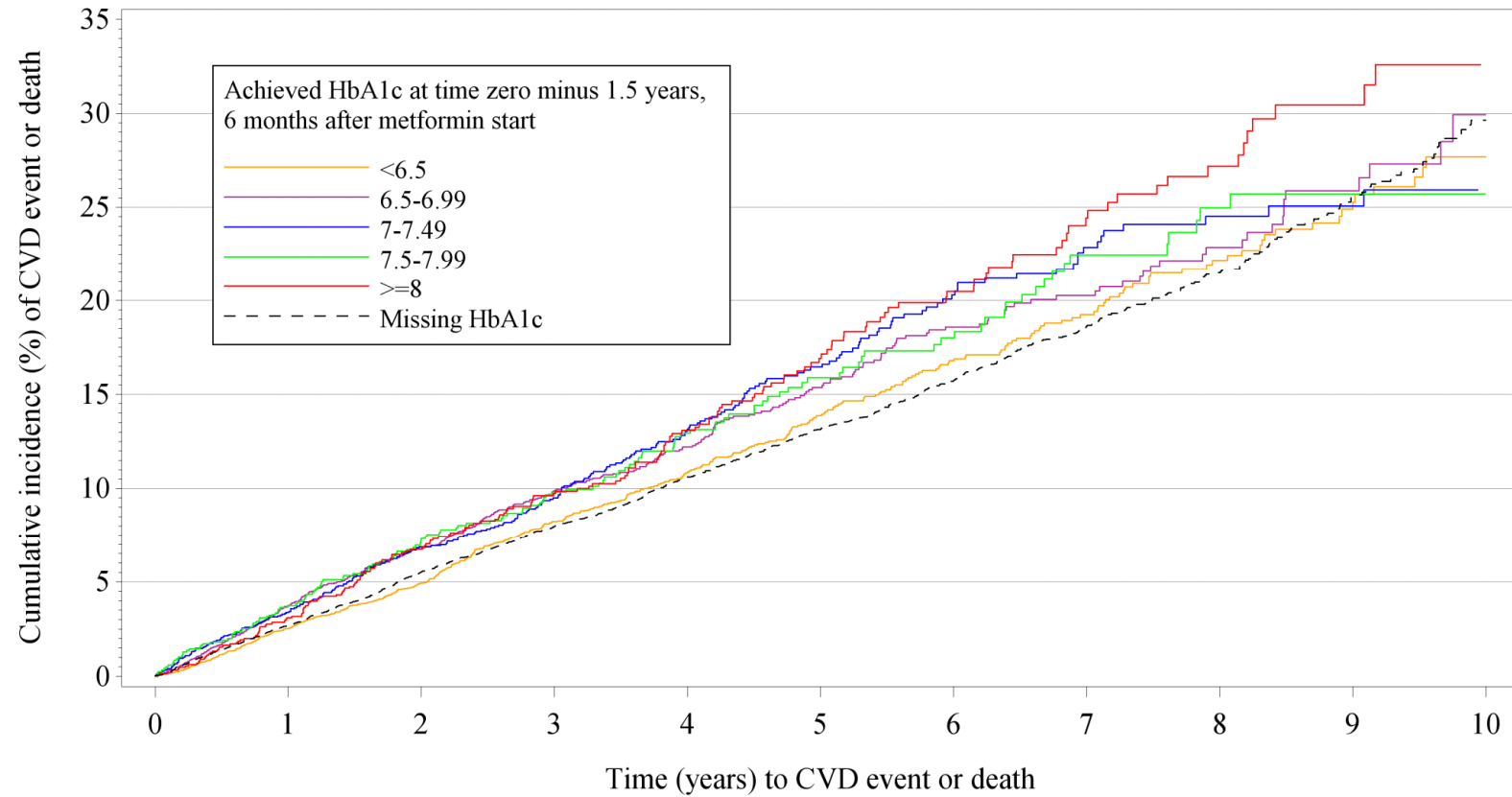
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Supplementary Figure S2. Adjusted hazard ratios (HRs) for combined outcome event (acute myocardial infarction, stroke, or death) by achieved HbA1c 6 months after metformin initiation, stratified by patient age and comorbidity. CVD=cardiovascular disease



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Supplementary Figure S3. Combined outcome event (acute myocardial infarction, stroke, or death), by achieved HbA1c level 6 months after metformin initiation. Follow-up starts 2 years after metformin initiation. CVD=cardiovascular disease.



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Supplementary Figure S4. Combined outcome event (acute myocardial infarction, stroke, or death), by achieved HbA1c level 6 months after metformin initiation. Restriction to patients with at least 5 years of follow-up time. Follow-up starts 180 days after metformin initiation. CVD=cardiovascular disease.

