

Impact of lower vs higher LDL cholesterol targets on cardiovascular events after ischemic stroke in diabetic patients

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Supplemental Table I. Hazard ratio of baseline factors to primary outcome and interaction between diabetic and non-diabetic patients

	Diabetics		Non-diabetics		Interaction p-value*
	HR (95% CI)*	p-value*	HR (95% CI)*	p-value*	
Age, per 10 years increase	1.26 (0.99-1.60)	0.055	1.23 (1.08-1.39)	0.001	0.84
Male sex	0.89 (0.53-1.49)	0.66	1.15 (0.85-1.56)	0.35	0.40
Body-mass index, per 4 units increase	1.05 (0.99-1.11)	0.13	0.95 (0.97-1.05)	0.32	0.10
Ischemic stroke as entry event	1.00 (0.46-2.18)	1.00	1.29 (0.87-1.91)	0.21	0.57
Time since entry event, days, per 4 days	1.00 (0.83-1.06)	0.91	0.99 (0.94-1.04)	0.64	0.84
Medical history					
Hypertension	2.13 (0.98-4.65)	0.058	1.25 (0.93-1.69)	0.15	0.21
Dyslipidemia	0.84 (0.48-1.46)	0.52	1.14 (0.84-1.56)	0.39	0.33
Former smoker	1.35 (0.81-2.25)	0.25	0.69 (0.48-1.00)	0.049	0.037
Current smoker	0.66 (0.37-1.17)	0.15	1.37 (1.03-1.83)	0.031	0.025
Stroke or TIA	0.75 (0.36-1.56)	0.44	1.99 (1.38-2.88)	<0.001	0.020
Coronary artery disease	1.89 (1.16-3.08)	0.010	2.12 (1.56-2.89)	<0.001	0.70
Lipids, mg/dL					
LDL-c, per 39 mg/dL increase	0.73 (0.57-0.93)	0.011	0.90 (0.77-1.04)	0.16	0.16
LDL change between baseline and 1 year, per 39 mg/dL decrease	0.76 (0.57-0.99)	0.045	0.89 (0.77-1.04)	0.13	0.18
HDL-c, per 18 mg/dL increase	0.96 (0.74-1.25)	0.76	0.99 (0.86-1.14)	0.90	0.84
Total cholesterol, per 39 mg/dL increase	0.82 (0.67-1.00)	0.054	0.91 (0.81-1.03)	0.14	0.38
Triglycerides, per 60 mg/dL increase	1.05 (0.92-1.20)	0.49	1.01 (0.89-1.14)	0.89	0.68
Atherogenic dyslipidemia ⁽¹⁾	1.19 (0.67-2.11)	0.55	0.70 (0.37-1.32)	0.27	0.22
Atherogenic dyslipidemia ⁽²⁾	1.07 (0.66-1.73)	0.78	1.07 (0.77-1.49)	0.69	1.00
Systolic blood pressure, per 10 mmHg increase	1.10 (1.00-1.21)	0.048	1.05 (0.98-1.11)	0.17	0.38
Diastolic blood pressure, per 5 mmHg increase	1.03 (0.95-1.12)	0.49	0.99 (0.93-1.04)	0.57	0.38
Glucose, per 2 mmol/L increase	1.08 (0.96-1.23)	0.20	1.01 (0.87-1.18)	0.86	0.50
Hemoglobin A1c, per 1%increase	0.93 (0.81-1.07)	0.28	0.83 (0.62-1.10)	0.18	0.48
TTR >50%	0.64 (0.38-1.08)	0.095	0.97 (0.72-1.29)	0.81	0.17

⁽¹⁾ Define as triglycerides >200 mg/dL and HDL ≤40 mg/dL for men (HDL ≤50 mg/dL for women);

⁽²⁾ Define as triglycerides >150 mg/dL and HDL ≤50 mg/dL

Supplemental table II. Multivariable analysis for primary outcome in diabetic and non-diabetic patients

	HR (95% CI)	p-value
Coronary artery disease	1.89 (1.42-2.52)	<0.001
Age	1.27 (1.11-1.46)	0.001
Current smoker		
Diabetic patients	1.06 (0.49-2.26)	0.89
Non-diabetic patients	1.76 (1.22-2.54)	0.003
Randomization group <70 mg/dL	0.72 (0.56-0.94)	0.014
Systolic blood pressure, per 10 mmHg increase	1.04 (0.99-1.10)	0.13
Stroke or TIA		
Diabetic patients	0.75 (0.33-1.76)	0.50
Non-diabetic patients	1.62 (1.08-2.43)	0.021
Former smoker		
Diabetic patients	1.30 (0.69-2.45)	0.42
Non-diabetic patients	0.77 (0.51-1.15)	0.20
LDL-c at baseline, per 39 mg/dL increase	0.90 (0.84-1.09)	0.70
LDL change between baseline and 1 year, per 39 mg/dL decrease	1.11 (0.84-1.52)	0.43
TTR >50%	0.79 (0.60-1.05)	0.11

Supplemental Table III. Univariable analysis of baseline characteristics for newly diagnosed diabetes in non-diabetic patients at baseline

Characteristics	Newly diagnosed diabetes		p-value
	Yes (n=178)	No (n=1977)	
Age, years	65.8 (10.3)	67.0 (11.7)	0.39
Male sex, no/total no, (%)	135/178 (75.8)	1288/1977 (65.2)	0.009
Body-mass index, median (IQR)	26.8 (24.5-29.1)	25.3 (23.1-28.0)	0.002
Entry event			0.70
Ischemic stroke	149/178 (83.7)	1652/1973 (83.7)	
TIA	29/178 (16.3)	321/1973 (16.3)	
Time since entry event, days, median (IQR)	6 (4-10)	6 (4-10)	0.24
Medical history			
Hypertension, no/total no, (%)	121/172 (70.4)	1220/1925 (63.4)	0.037
Dyslipidemia, no/total no, (%)	116/164 (70.7)	1148/1826 (62.9)	0.079
Former smoker, no/total no, (%)	45/178 (25.3)	437/1972 (22.2)	0.46
Current smoker, no/total no, (%)	68/178 (38.2)	591/1972 (30.0)	0.021
Stroke or TIA, no/total no, (%)	21/176 (11.9)	201/1952 (10.3)	0.20
Coronary artery disease, no/total no, (%)	28/176 (15.9)	309/1947 (15.9)	0.97
Lipids, mg/dL			
LDL-c, mean (sd)	138 (37)	137 (37)	0.80
LDL change between baseline and 1 year	53 (43)	51 (43)	0.74
HDL-c, mean (sd)	46 (13)	52 (19)	<0.001
Total cholesterol, mean (sd)	211 (41)	212 (48)	0.28
Triglycerides, median (IQR)	139.5 (105.0-187.0)	115.0 (86.0-156.0)	<0.001
Atherogenic dyslipidemia ⁽¹⁾	22/178 (12.4)	130/1971 (6.6)	0.003
Atherogenic dyslipidemia ⁽²⁾	54/178 (30.3)	396/1971 (20.1)	0.002
Systolic blood pressure, mmHg, mean (sd)	143 (20)	140 (22)	0.069
Diastolic blood pressure, mmHg, mean (sd)	80 (13)	79 (13)	0.79
Glucose, mg/dL, median (IQR)	6.0 (5.5-6.6)	5.3 (4.9-5.9)	<0.001
Hemoglobin A1c, %, mean (sd)	6.4 (0.8)	5.7 (0.5)	<0.001
<70 mg/dL group, no/total no, (%)	98/178 (55.1)	972/1977 (49.2)	0.11

⁽¹⁾ Define as triglycerides >200 mg/dL and HDL ≤40 mg/dL for men (HDL ≤50 mg/dL for women);

⁽²⁾ Define as triglycerides >150 mg/dL and HDL ≤50 mg/dL

Supplemental Table IV. Multivariable analysis for newly diagnosed diabetes in non-diabetic patients at baseline

	HR (95% CI)	p-value
Hemoglobin A1c	1.85 (1.68-2.04)	<0.001
BMI, by 5 units	1.02 (1.01-1.04)	0.001
HDL	0.98 (0.97-0.99)	0.004
Hypertension	1.44 (1.03-2.02)	0.036
Randomization group <70 mg/dL	1.37 (1.01-1.86)	0.038
Current smoker	1.37 (0.99-1.89)	0.055
Male sex	1.39 (0.97-1.98)	0.071

Supplemental table V. Multivariable analysis for newly diagnosis diabetes in non-diabetic patients at baseline including significant baseline factors, smoking cessation and weight gain during follow-up

	HR (95% CI)	p-value
Hemoglobin A1c	1.79 (1.45-2.22)	<0.001
BMI, by 5 units	1.01 (0.99-1.04)	0.22
HDL	0.99 (0.97-1.02)	0.59
Hypertension	1.95 (0.98-3.91)	0.059
Randomization group <70 mg/dL	0.92 (0.52-1.62)	0.77
Current smoker	2.10 (0.95-4.62)	0.066
Male sex	0.80 (0.42-1.54)	0.50
Weight gain during trial	1.01 (0.99-1.03)	0.20
Smoking cessation	1.80 (0.62-5.17)	0.28