

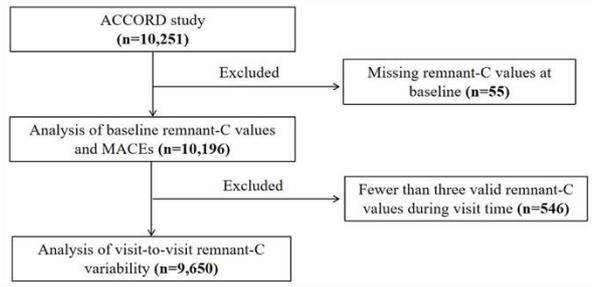
Supplemental Files

Supplemental Figure 1. Flowchart for selecting the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study participants for analysis. Enrollment chart demonstrating patients included in the final sample. ACCORD: Action to Control Cardiovascular Risk in Diabetes; Remnant-C: Remnant cholesterol; MACEs: Major adverse cardiovascular events.

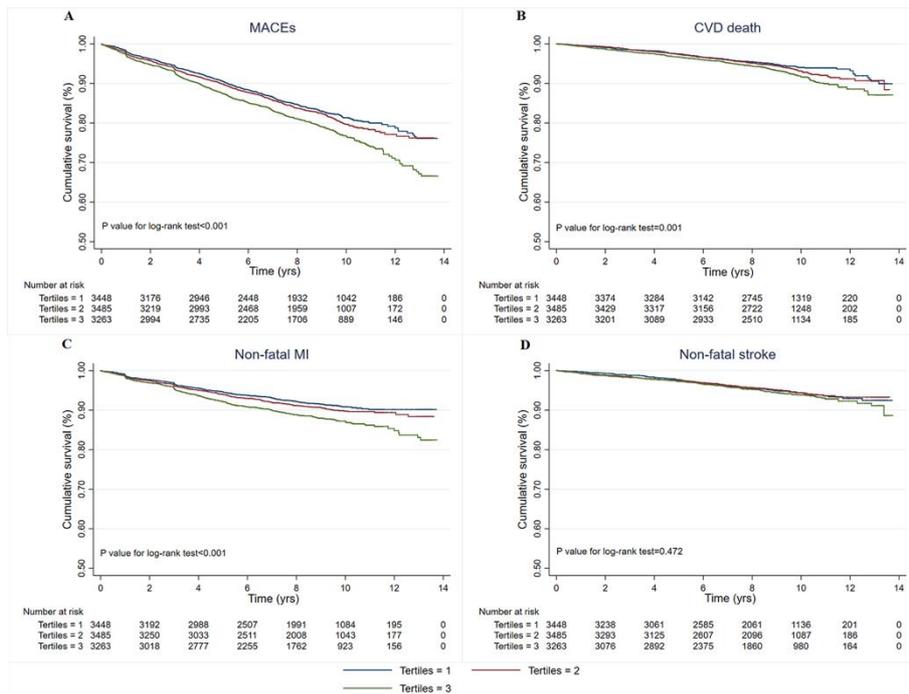
Supplemental Figure 2. Kaplan–Meier survival curves for primary and secondary outcomes according to tertiles of baseline remnant-C (A) MACEs: Major adverse cardiovascular events; (B) CVD death: Cardiovascular disease (CVD) death; (C) Non-fatal MI: Non-fatal myocardial infarction (MI). (D) Non-fatal stroke.

Supplemental Figure 3. Subgroup analyses of the relationship between remnant-C level and MACEs. The study population was stratified by age, sex, body mass index (BMI), and CVD history. Adjustments for sex, age, education, years of hypertension diagnosis, SBP, DBP, heart rate, depression, smoking habit, alcohol consumption, BMI, previous cardiovascular history, plasma glucose level, eGFR, HbA1c, LDL-C level, biguanide treatment, statin treatment, and insulin treatment were made.

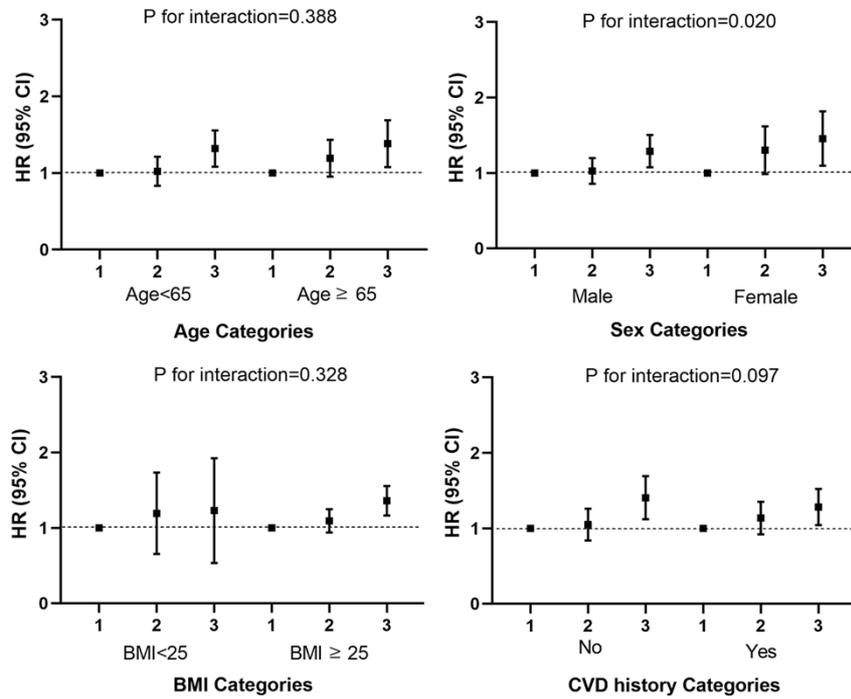
Supplemental Figure 4. Receiver operating characteristic (ROC) analysis of major adverse cardiovascular events (MACEs). Model 1 included clinically conventional risk factors for cardiovascular events (sex, age, smoking, BMI, blood glucose, and glycated hemoglobin) and remnant-C level, whereas model 2 included only clinically common risk factors for cardiovascular events.



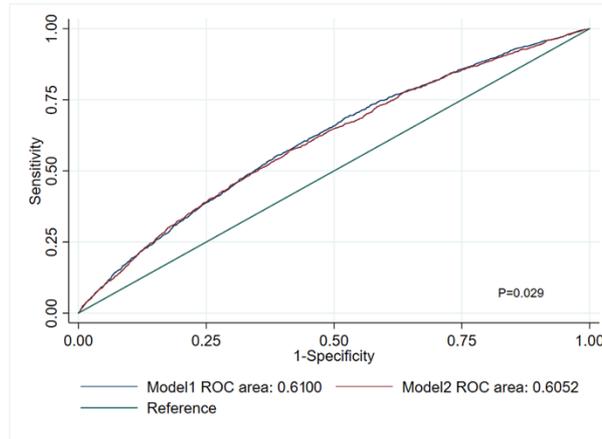
Supplemental Figure 1. Study participant selection from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study. The chart depicts the subjects included in the final sample group.



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Supplemental Table 1. Correlation testing of baseline characteristics

	Remnant-C	Triglycerides	Cholesterol	LDL-C	HDL-C	Non-HDL-C
Remnant-C	1.000					
Triglycerides	0.955***	1.000				
Cholesterol	0.460***	0.421***	1.000			
LDL-C	-0.017*	-0.039***	0.843***	1.000		
HDL-C	-0.389***	-0.372***	0.177***	0.155***	1.000	
Non-HDL-C	0.574***	0.530***	0.961***	0.809***	-0.102***	1.000

Remnant-C, remnant cholesterol; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol

*** signifies $P < 0.001$

Supplemental Table 2. Baseline characteristics by groups of LDL-cholesterol and remnant-cholesterol cutoff levels (mg/dL)

	Total (N=10,196)	LDL-C ≤100 mg/dL & remnant-C <31 mg/dL (N=2444; 23.97%)	LDL-C ≤100 mg/dL & remnant-C ≥31 mg/dL (N=2502; 24.54%)	LDL-C >100 mg/dL & remnant-C <31 mg/dL (N=2537; 24.88%)	LDL-C >100 mg/dL & remnant-C ≥31 mg/dL (N=2713; 26.61%)	P-value
Age, years (mean ± SD)	62.77±6.63	63.78±6.90	62.69± 6.56	62.70±6.69	61.98±6.27	<0.001
Sex No. (%)						<0.001
Female	3928 (38.52)	828 (33.88)	802 (32.05)	1111 (43.79)	1187 (43.75)	
Male	6268 (61.48)	1616 (66.12)	1700 (67.95)	1426 (56.21)	1526 (56.25)	
Education, No. (%)						
Less than high school	1502 (14.73)	389 (15.92)	288 (11.51)	431 (16.99)	394 (14.52)	<0.001
High school graduate or GED	2692 (26.40)	648 (26.51)	647 (25.86)	684 (26.96)	713 (26.28)	0.844
Some college	3343 (32.79)	764 (31.26)	882 (35.25)	794 (31.30)	903 (33.28)	0.006
College degree or higher	2652 (26.01)	643 (26.31)	684 (27.34)	624 (24.60)	701 (25.84)	0.166

Living alone, No. (%)	2065 (20.65)	472 (19.31)	476 (19.02)	555 (21.88)	562 (20.72)	<0.001
Depression, No. (%)	2412 (23.66)	483 (19.76)	677 (27.06)	499 (19.67)	753 (27.76)	<0.001
History of CVD, No. (%)	3586 (35.17)	957 (39.16)	1029 (41.13)	741 (29.21)	859 (31.66)	<0.001
Duration of hypertension, y (mean \pm SD)	10.23 \pm 9.58	10.19 \pm 9.40	10.88 \pm 9.66	9.74 \pm 9.48	10.12 \pm 9.73	0.003
Cigarette-smoking status, No. (%)						<0.001
Yes	5925 (58.11)	1438 (58.84)	1544 (61.71)	1365 (53.80)	1578 (58.16)	
No	4271 (41.89)	1006 (41.16)	958 (38.29)	1172 (46.20)	1135 (41.84)	
Alcohol use status, No. (%)						<0.001
Yes	2434 (23.87)	612 (25.04)	612 (24.46)	592 (23.33)	618 (22.78)	
No	7757 (76.08)	1831 (74.92)	1887 (75.42)	1944 (76.63)	2095 (77.22)	
BMI, (mean \pm SD)	32.22 \pm 5.42	31.48 \pm 5.41	33.00 \pm 5.11	31.64 \pm 5.67	32.71 \pm 5.32	<0.001
Blood pressure, mmHg (mean \pm SD)						
Systolic	136.35 \pm 17.11	135.05 \pm 17.28	134.23 \pm 16.58	138.45 \pm 16.79	137.50 \pm 17.40	<0.001
Diastolic	74.88 \pm 10.66	72.75 \pm 10.73	74.13 \pm 10.36	75.78 \pm 10.27	76.66 \pm 10.84	<0.001
Heart rate, bpm (mean \pm SD)	72.66 \pm 11.82	71.30 \pm 11.77	72.53 \pm 12.01	72.62 \pm 11.60	74.02 \pm 11.74	<0.001

Medication use, No. (%)						
Insulin	3565 (34.96)	1037 (42.43)	815 (32.57)	953 (37.56)	760 (28.01)	<0.001
Metformin	6519 (63.94)	1642 (67.18)	1795 (71.74)	1447 (57.04)	1635 (60.27)	<0.001
Statins	6468 (63.44)	2045 (83.67)	1948 (77.86)	1261 (49.70)	1214 (44.75)	<0.001
Cholesterol absorption inhibitors	207 (2.03)	50 (2.05)	59 (2.36)	39 (1.54)	59 (2.17)	0.192
Glycated hemoglobin, % (mean ± SD)	8.30±1.06	8.16±0.99	8.23±0.96	8.35±1.09	8.45±1.14	<0.001
Fasting plasma glucose, mg/dL (mean ± SD)	175.19±56.17	161.30±52.17	182.46±54.80	169.12±55.38	186.70±58.17	<0.001
eGFR, mL/min/1.73 m ² (mean ± SD)	91.05±27.15	89.96±23.37	89.99±31.58	93.32±25.73	90.89±27.09	<0.001
Remnant cholesterol, mg/dL (mean ± SD)	36.54±24.35	20.15±5.96	53.17±29.90	21.29±5.59	50.23±21.00	<0.001
Plasma triglycerides, mg/dL (mean ± SD)	190.11±148.4	100.82±29.81	285.67±206.13	106.48±27.94	260.69±122.19	<0.001
Total plasma cholesterol, mg/dL (mean ± SD)	183.29±41.85	144.36±19.17	165.51±31.03	196.61±27.37	222.36±36.25	<0.001
Plasma LDL-C, mg/dL (mean ± SD)	104.89±33.93	79.33±13.96	76.26±16.50	127.77±23.37	132.95±27.63	<0.001

Plasma HDL-C, mg/dL (mean ± SD)	41.87±11.62	44.88±11.86	36.08±8.67	47.55±12.59	39.18±9.33	<0.001
Plasma Non-HDL-C, mg/dL (mean ± SD)	141.44±41.41	99.48±15.41	129.44±31.41	149.06±24.48	183.18±35.29	<0.001
Incident MACEs, No. (%)	1815 (17.80)	376 (15.38)	465 (18.59)	422 (16.63)	552 (20.35)	<0.001

GED, general education development; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MACEs, major adverse cardiovascular events.

Supplemental Table 3. Risk of MACEs based on LDL-C and remnant-C levels

	Events/No. at risk	Unadjusted		Model 1		Model 2		Model 3	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Cut-offs: LDL-C 130 mg/dL; Remnant-C 49 mg/dL									
LDL-C \leq 130 mg/dL & Remnant-C <49 mg/dL	1063/6308								
LDL-C \leq 130 mg/dL & Remnant-C \geq 49 mg/dL	329/1687	1.20 (1.06- 1.36)	0.004	1.23 (1.07- 1.42)	0.005	1.22 (1.05- 1.41)	0.009	1.24 (1.07- 1.43)	0.005
LDL-C >130 mg/dL & Remnant-C <49 mg/dL	307/1687	1.09 (0.96- 1.23)	0.201	1.27 (1.09- 1.47)	0.002	0.97 (0.77- 1.22)	0.788	0.96 (0.76- 1.21)	0.720
LDL-C >130 mg/dL & Remnant-C \geq 49 mg/dL	127/569	1.38 (1.15- 1.66)	0.001	1.49 (1.21- 1.83)	0.000	0.99 (0.74- 1.35)	0.989	1.02 (0.76- 1.38)	0.873

LDL-C \leq 100 mg/dL & Remnant-C \geq 31 mg/dL	465/2502	1.23 (1.07- 1.40)	0.003	1.20 (1.02- 1.40)	0.024	1.17 (0.99- 1.38)	0.051	1.22 (1.04- 1.44)	0.015
LDL-C >100 mg/dL & Remnant-C <31 mg/dL	422/2537	1.06 (0.93- 1.22)	0.381	1.22 (1.04- 1.43)	0.017	0.98 (0.76- 1.25)	0.865	0.99 (0.77- 1.27)	0.913
LDL-C >100 mg/dL & Remnant-C \geq 31 mg/dL	552/2713	1.35 (1.18- 1.54)	<0.001	1.57 (1.35- 1.83)	<0.001	1.38 (1.10- 1.73)	0.006	1.37 (1.09- 1.73)	0.007
Cut-offs: LDL-C 70 mg/dL; Remnant-C 17 mg/dL									
LDL-C \leq 70 mg/dL & Remnant-C <17 mg/dL	20/185								
LDL-C \leq 70 mg/dL & Remnant-C \geq 17 mg/dL	208/1163	1.65 (0.05- 2.61)	0.032	1.58 (0.94- 2.66)	0.086	1.45 (0.86- 2.46)	0.168	1.49 (0.88- 2.53)	0.141

LDL-C >70 mg/dL & Remnant-C <17 mg/dL	159/1117	1.28 (0.81- 2.04)	0.293	1.36 (0.79- 2.34)	0.263	1.28 (0.69- 2.37)	0.442	1.35 (0.72- 2.53)	0.351
LDL-C >70 mg/dL & Remnant-C ≥17 mg/dL	1428/7731	1.67 (1.07- 2.59)	0.023	1.74 (1.06- 2.86)	0.028	1.37 (0.82- 2.27)	0.225	1.40 (0.85- 2.33)	0.190

Model 1: Adjusted for sex, age, education, years of hypertension diagnosis, systolic blood pressure, diastolic blood pressure, heart rate, depression, smoking habits, alcohol consumption, BMI, and previous cardiovascular history.

Model 2: Adjusted for model 1 covariables plus plasma glucose level, eGFR, HbA1c, and LDL-C level.

Model 3: Adjusted for model 2 covariables plus treatment with biguanide, statins, and insulin.