SUPPLEMENTAL MATERIAL

Appendix

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Table S1. Baseline characteristics according to the smoking status.

Baseline characteristics	Never smokers		Former smokers		Current smokers		*P* value*
	No.	Value	No.	Value	No.	Value	
Stages of chronic kidney disease †	955		1035		428		0.353
Stage 3a		229 (24.0)		258 (24.9)		96 (22.4)	
Stage 3b		99 (10.4)		115 (11.1)		33 (7.7)	
Stage 4		35 (3.7)		37 (3.6)		11 (2.6)	
Stage 5		34 (3.6)		39 (3.8)		13 (3.0)	
Dialysis	955	31 (3.3)	1035	36 (3.5)	428	13 (3.0)	0.903
Multi-vessel or LMT disease	955	264 (27.6)	1035	373 (36.0)	428	157 (36.7)	<0.001
NYHA class III or IV	955	113 (11.8)	1035	88 (8.5)	428	51 (11.9)	0.028
Previous PCI	955	192 (20.1)	1035	321 (31.0)	428	96 (22.4)	<0.001
Previous CABG	955	32 (3.4)	1035	49 (4.7)	428	8 (1.9)	0.024
Previous CAD (MI, PCI, or CABG)	955	226 (23.7)	1035	369 (35.7)	428	106 (24.8)	<0.001
Previous cardiovascular events‡	955	387 (40.5)	1035	538 (52.0)	428	173 (40.4)	<0.001
Family history of cardiovascular events	955	258 (27.0)	1035	320 (30.9)	428	113 (26.4)	0.086
Systolic blood pressure, mean (SD), mmHg	955	126 (18)	1035	128 (18)	428	126 (18)	0.113
Diastolic blood pressure, mean (SD), mmHg	955	70 (12)	1035	70 (12)	428	71 (13)	0.368
Pulse rate, mean (SD), beats per minute	955	70 (14)	1035	70 (13	428	70 (13)	0.951
LDL-cholesterol, mean (SD), mg/dL	932	107 (32)	1013	102 (29)	421	107 (32)	<0.001
HDL-cholesterol, mean (SD), mg/dL	925	58 (17)	1010	53 (15)	418	50 (15)	<0.001
Triglycerides, median (IQR), mg/dL	938	104 (75-146)	1019	115 (82-166)	425	125 (94-189)	<0.001
Fasting glucose, median (IQR), mg/dL	938	108 (95-135)	1024	111 (97-144)	419	111 (96-147)	0.022

Hemoglobin A1c, median (IQR), %	899	6.0 (5.6-6.9)	989	6.1 (5.7-7.1)	418	6.1 (5.6-7.1)	0.033
Creatinine, median (IQR), mg/dL	955	0.8 (0.6-1.0)	1035	0.9 (0.8-1.1)	428	0.9 (0.7-1.0)	<0.001
Hemoglobin, mean (SD), g/dL	952	12.6 (1.7)	1033	13.1 (1.8)	427	13.5 (2.0)	<0.001
Hematocrit, mean (SD), %	951	38.0 (5.0)	1033	39.4 (5.2)	427	40.5 (5.9)	<0.001
Uric acid, mean (SD), mg/dL	928	5.7 (1.7)	1004	6.0 (1.7)	415	6.2 (1.8)	<0.001
Anti-hypertensive drug use							
RASI	955	554 (58.0)	1035	626 (60.5)	428	252 (58.9)	0.527
ACEI	955	135 (14.1)	1035	176 (17.0)	428	77 (18.0)	0.106
ARB	955	440 (46.1)	1035	474 (45.8)	428	189 (44.2)	0.794
β-blocker	955	291 (30.5)	1035	297 (28.7)	428	127 (29.7)	0.686
Any lipid-lowering drug use	955	537 (56.2)	1035	610 (58.9)	428	235 (54.9)	0.278
Any hypoglycemic drug use	955	273 (28.6)	1035	342 (33.0)	428	145 (33.9)	0.049
Oral hypoglycemic drugs	955	223 (23.4)	1035	272 (26.3)	428	108 (25.2)	0.316
Insulin	955	103 (10.8)	1035	124 (12.0)	428	58 (13.6)	0.326
Any anti-platelet drug use	955	541 (56.7)	1035	706 (68.2)	428	262 (61.2)	<0.001
Any anti-coagulant drugs	955	155 (16.2)	1035	166 (16.0)	428	62 (14.5)	0.695
Warfarin	955	128 (13.4)	1035	147 (14.2)	428	57 (13.3)	0.842

Values are expressed as number (percentage) unless otherwise indicated. LMT indicates left main trunk; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; SD, standard deviation; LDL, low-density lipoprotein; HDL, high-density lipoprotein; IQR, interquartile range; RASI, renin angiotensin system inhibitors; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers. *The *P* value is for comparison between groups, and is based on the χ^2 test of independence for categorical variables, and the analysis of variance or Kruskal-Wallis for continuous variables.[†]Chronic kidney disease is defined as an estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 m^2 of body surface area. eGFRs of stages. 3a, 3b, 4, and 5 are defined as follows: stage 3a, 45–59 ml/min/1.73 m^2; stage 3b, 30–44 ml/min/1.73 m^2; stage 4, 15–29 ml/min/1.73 m^2; stage 5, ≤14ml/min/1.73 m^2. [‡] Previous cardiovascular events include myocardial infarction, stroke, heart failure hospitalization, and coronary revascularization

Table S2. Baseline characteristics and incidence of outcomes according to quartiles of GDF-15 in the entire cohort.

Baseline characteristics and incidence of events	Quartile 1		Quartile 2		Quartile 3		Quartile 4		*P* value*
	No.	Value	No.	Value	No.	Value	No.	Value	
Baseline characteristics									
Age, mean (SD), y	605	63.6 (11.5)	604	70.5 (9.0)	604	73.9 (8.0)	605	74.3 (9.3)	<0.001
Male	605	376 (62.2)	604	402 (66.6)	604	424 (70.2)	605	422 (69.8)	0.010
Body mass index, mean (SD)	605	24.6 (3.8)	604	24.5 (4.0)	604	24.2 (3.8)	605	23.5 (4.0)	<0.001
Obesity†	605	253 (41.8)	604	242 (40.1)	604	231 (38.3)	605	210 (34.7)	0.070
Hypertension	605	421 (69.6)	604	457 (75.7)	604	472 (78.2)	605	493 (81.5)	<0.001
Dyslipidemia	605	387 (64.0)	604	383 (63.4)	604	381 (63.1)	605	315 (52.1)	<0.001
Diabetes	605	204 (33.7)	604	262 (43.4)	604	278 (46.0)	605	343 (56.7)	<0.001
Current smoker	605	97 (16.0)	604	104 (17.2)	604	111 (18.4)	605	116 (19.2)	0.505
Former smoker	605	224 (37.0)	604	257 (42.6)	604	295 (48.8)	605	259 (42.8)	<0.001
eGFR, mean (SD), ml/min/1.73 m^2	605	76.7 (17.5)	604	68.5 (17.3)	604	62.1 (16.3)	605	45.8 (24.3)	<0.001
Chronic kidney disease ‡	605	90 (14.9)	604	191 (31.6)	604	280 (46.4)	605	438 (72.4)	<0.001
Stages of chronic kidney disease	605		604		604		605		<0.001
Stage 3a		76 (12.6)		157 (26.0)		197 (32.6)		153 (25.3)	
Stage 3b		14 (2.3)		29 (4.8)		77 (12.8)		127 (21.0)	
Stage 4		0 (0.0)		3 (0.5)		6 (1.0)		74 (12.2)	
Stage 5		0 (0.0)		2 (0.3)		0 (0.0)		84 (13.9)	
Dialysis	605	0 (0.0)	604	1 (0.2)	604	0 (0.0)	605	79 (13.1)	<0.001
Gensini score, median (IQR)§	605	7.0 (0.0-24.3)	604	11.5 (2.5-34.0)	604	15.0 (4.0-39.9)	605	15.5 (4.0-47.5)	<0.001
Obstructive CAD	605	288 (47.6)	604	348 (57.6)	604	374 (61.9)	605	382 (63.1)	<0.001

Multi-vessel or LMT disease	605	149 (24.6)	604	180 (29.8)	604	218 (36.1)	605	247 (40.8)	<0.001
NYHA class III or IV	605	27 (4.5)	604	46 (7.6)	604	57 (9.4)	605	122 (20.2)	<0.001
Atrial fibrillation	605	30 (5.0)	604	53 (8.8)	604	72 (11.9)	605	106 (17.5)	<0.001
Malignancies	605	39 (6.5)	604	47 (7.8)	604	64 (10.6)	605	76 (12.6)	0.001
Anemia[ll]	605	95 (15.7)	604	152 (25.2)	604	232 (38.4)	605	403 (66.6)	<0.001
Previous MI	605	75 (12.4)	604	93 (15.4)	604	89 (14.7)	605	97 (16.0)	0.301
Previous PCI	605	133 (22.0)	604	167 (27.7)	604	168 (27.8)	605	141 (23.3)	0.035
Previous CABG	605	13 (2.2)	604	15 (2.5)	604	21 (3.5)	605	40 (6.6)	<0.001
Previous CAD (MI, PCI, or CABG)	605	147 (24.3)	604	184 (30.5)	604	189 (31.3)	605	181 (29.9)	0.030
Previous stroke	605	51 (8.4)	604	91 (15.1)	604	97 (16.1)	605	114 (18.8)	<0.001
Precious CHF hospitalization	605	23 (3.8)	604	41 (6.8)	604	56 (9.3)	605	133 (22.0)	<0.001
Previous cardiovascular events[#]	605	210 (34.7)	604	283 (46.9)	604	283 (46.9)	605	322 (53.2)	<0.001
Family history of cardiovascular events	605	193 (31.9)	604	183 (30.3)	604	174 (28.8)	605	141 (23.3)	0.006
Systolic blood pressure, mean (SD), mmHg	605	127 (17)	604	127 (18)	604	126 (18)	605	127 (20)	0.900
Diastolic blood pressure, mean (SD), mmHg	605	73 (12)	604	71 (13)	604	70 (12)	605	69 (12)	<0.001
Pulse rate, mean (SD), beats per minute	605	68 (11)	604	70 (14)	604	70 (13)	605	73 (14)	<0.001
LDL-cholesterol, mean (SD), mg/dL	581	112 (31)	593	107 (29)	598	104 (30)	594	96 (30)	<0.001
HDL-cholesterol, mean (SD), mg/dL	587	56 (16)	593	55 (16)	585	54 (16)	588	52 (16)	<0.001
Triglycerides, median (IQR), mg/dL	592	125 (88-186)	596	115 (83-163)	596	109 (80-156)	598	101 (74-144)	<0.001

Fasting glucose, median (IQR), mg/dL	594	107 (95-131)	595	111 (96-144)	598	112 (98-140)	594	112 (94-149)	0.027
Hemoglobin A1c, median (IQR), %	570	5.9 (5.6-6.6)	578	6.1 (5.7-7.1)	586	6.1 (5.7-7.0)	572	6.2 (5.7-7.1)	<0.001
Creatinine, median (IQR), mg/dL	605	0.7 (0.6-0.9)	604	0.8 (0.7-0.9)	604	0.9 (0.7-1.0)	605	1.1 (0.9-1.6)	<0.001
Hemoglobin, mean (SD), g/dL	604	13.8 (1.4)	600	13.5 (1.5)	604	13.0 (1.6)	604	11.7 (2.0)	<0.001
Hematocrit, mean (SD), %	604	41.1 (4.2)	600	40.3 (4.5)	604	39.1 (4.7)	603	35.5 (6.0)	<0.001
Uric acid, mean (SD), mg/dL	588	5.6 (1.5)	589	5.7 (1.6)	591	6.0 (1.7)	579	6.4 (1.9)	<0.001
NT-proBNP, median (IQR), pg/mL	605	91 (41-210)	604	151 (61-434)	604	210 (88-726)	605	886 (247-2782)	<0.001
cTnI, median (IQR), pg/mL	605	0.0 (0.0–1.0)	604	0.0 (0.0–6.0)	604	0.0 (0.0–11.0)	605	9.0 (0.0–33.5)	<0.001
hs-CRP, median (IQR), mg/L	605	0.5 (0.2-1.6)	604	0.8 (0.3-2.2)	604	1.1 (0.3-3.3)	605	2.0 (0.5-6.2)	<0.001
GDF-15, median (IQR), pg/mL	605	690 (549-803)	604	1102 (1010-1206)	604	1561 (1440-1740)	605	2774 (2247-4160)	<0.001
Anti-hypertensive drug use	605	456 (75.4)	604	489 (81.0)	604	492 (81.5)	605	530 (87.6)	<0.001
RASI	605	302 (49.9)	604	347 (57.5)	604	371 (61.4)	605	412 (68.1)	<0.001
ACEI	605	76 (12.6)	604	87 (14.4)	604	94 (15.6)	605	131 (21.7)	<0.001
ARB	605	234 (38.7)	604	268 (44.4)	604	285 (47.2)	605	316 (52.2)	<0.001
β-blocker	605	150 (24.8)	604	186 (30.8)	604	166 (27.5)	605	213 (35.2)	<0.001
Any lipid-lowering drug use	605	346 (57.2)	604	352 (58.3)	604	362 (59.9)	605	322 (53.2)	0.110
Statin use	605	310 (51.2)	604	318 (52.7)	604	319 (52.8)	605	275 (45.5)	0.034
Any hypoglycemic drug use	605	149 (24.6)	604	185 (30.6)	604	202 (33.4)	605	224 (37.0)	<0.001
Oral hypoglycemic drugs	605	126 (20.8)	604	155 (25.7)	604	162 (26.8)	605	160 (26.5)	0.057
Insulin	605	45 (7.4)	604	68 (11.3)	604	69 (11.4)	605	103 (17.0)	<0.001
Any anti-platelet drug use	605	362 (59.8)	604	396 (65.6)	604	386 (63.9)	605	365 (60.3)	0.114
Aspirin use	605	340 (56.2)	604	349 (57.8)	604	337 (55.8)	605	314 (51.9)	0.205
Any anti-coagulant drugs	605	54 (8.9)	604	82 (13.6)	604	108 (17.9)	605	139 (23.0)	<0.001

Warfarin	605	44 (7.3)	604	69 (11.4)	604	92 (15.2)	605	127 (21.0)	<0.001
Incidence of events, no. (/1000 person-years)									
All-cause death	605	20 (11.3)	604	22 (12.4)	604	51 (29.1)	605	161 (102.6)	–
Cardiovascular death	605	6 (3.4)	604	8 (4.5)	604	12 (6.9)	605	62 (39.5)	–
Myocardial infarction	605	3 (1.7)	604	3 (1.7)	604	6 (3.4)	605	9 (5.8)	–
Stroke	605	17 (9.7)	604	15 (8.6)	604	13 (7.5)	605	24 (15.5)	–
First MACE**	605	25 (14.3)	604	25 (14.3)	604	29 (16.8)	605	86 (55.9)	–

Values are expressed as number (percentage) unless otherwise indicated. The quartiles of GDF-15 levels were as follows: quartile 1, ≤902.0; quartile 2, 902.6–1322.1; quartile 3, 1322.5–1980.2; quartile 4, ≥1980.3 pg/mL. GDF-15 indicates growth differentiation factor-15; SD, standard deviation; eGFR, estimated glomerular filtration rate; CAD, coronary artery disease; IQR, interquartile range; LMT, left main trunk; NYHA, New York Heart Association; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CHF, congestive heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; cTnI, contemporary sensitive cardiac troponin I; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; RASI, renin angiotensin system inhibitors; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; MACE, major adverse cardiovascular events.

*The *P* value is for comparison between groups, and is based on the χ^2 test of independence for categorical variables, and the analysis of variance or Kruskal-Wallis for continuous variables.

†Obesity is defined as a body mass index of 25 or more.

‡Chronic kidney disease is defined as an estimated GFR of less than 60 ml/min/1.73 m^2 of body surface area. eGFRs of stages 3a, 3b, 4, and 5 are defined as follows: stage 3a, 45–59 ml/min/1.73 m^2; stage 3b, 30–44 ml/min/1.73 m^2; stage 4, 15–29 ml/min/1.73 m^2; stage 5, ≤14 ml/min/1.73 m^2.

§The Gensini score represents the angiographic severity of coronary artery disease employing a nonlinear points system for degree of luminal narrowing.

‖Anemia is defined as a hemoglobin level of less than 13 g/dL in men and less than 12 g/dL in women.

#Previous cardiovascular events include myocardial infarction, stroke, heart failure hospitalization, and coronary revascularization.

**MACE is defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

Table S3. Baseline characteristics and incidence of outcomes according to quartiles of GDF-15 in never smokers.

Baseline characteristics and incidence of events	Quartile 1		Quartile 2		Quartile 3		Quartile 4		*P* value*
	No.	Value	No.	Value	No.	Value	No.	Value	
Baseline characteristics									
Age, mean (SD), y	239	64.1 (11.8)	238	71.9 (8.7)	239	75.0 (8.3)	239	75.0 (10.1)	<0.001
Male	239	91 (38.1)	238	89 (37.4)	239	94 (39.3)	239	97 (40.6)	0.897
Body mass index, mean (SD)	239	24.3 (4.3)	238	24.3 (3.9)	239	24.0 (3.9)	239	23.7 (4.4)	0.257
Obesity†	239	96 (40.2)	238	92 (38.7)	239	86 (36.0)	239	91 (38.1)	0.823
Hypertension	239	162 (67.8)	238	175 (73.5)	239	179 (74.9)	239	188 (78.7)	0.057
Dyslipidemia	239	136 (56.9)	238	148 (62.2)	239	163 (68.2)	239	116 (48.5)	<0.001
Diabetes	239	68 (28.5)	238	88 (37.0)	239	100 (41.8)	239	133 (55.7)	<0.001
Current smoker	239	0 (0.0)	238	0 (0.0)	239	0 (0.0)	239	0 (0.0)	–
Former smoker	239	0 (0.0)	238	0 (0.0)	239	0 (0.0)	239	0 (0.0)	–
eGFR, mean (SD), ml/min/1.73 m^2	239	76.5 (16.9)	238	68.5 (16.9)	239	61.1 (16.6)	239	44.9 (24.1)	<0.001
Chronic kidney disease ‡	239	36 (15.1)	238	78 (32.8)	239	108 (45.2)	239	175 (73.2)	<0.001
Stages of chronic kidney disease	239		238		239		239		<0.001
Stage 3a		30 (12.6)		66 (27.7)		77 (32.2)		56 (23.4)	
Stage 3b		6 (2.5)		12 (5.0)		26 (10.9)		55 (23.0)	
Stage 4		0 (0.0)		0 (0.0)		5 (2.1)		30 (12.6)	
Stage 5		0 (0.0)		0 (0.0)		0 (0.0)		34 (14.2)	
Dialysis	239	0 (0.0)	238	0 (0.0)	239	0 (0.0)	239	31 (13.0)	<0.001
Obstructive CAD	239	93 (38.9)	238	117 (49.2)	239	137 (57.3)	239	143 (59.8)	<0.001
Multi-vessel or LMT disease	239	40 (16.7)	238	57 (24.0)	239	82 (34.3)	239	85 (35.6)	<0.001

Gensini score, median (IQR)[§]	239	3.0 (0.0-19.0)	238	7.0 (1.0-21.1)	239	12.0 (3.0-36.5)	239	13.0 (3.0-42.5)	<0.001
NYHA class III or IV	239	15 (6.3)	238	16 (6.7)	239	30 (12.6)	239	52 (21.8)	<0.001
Atrial fibrillation	239	9 (3.8)	238	23 (9.7)	239	37 (15.5)	239	48 (20.1)	<0.001
Malignancies	239	16 (6.7)	238	17 (7.1)	239	11 (4.6)	239	24 (10.0)	0.142
Anemia[‖]	239	37 (15.5)	238	70 (29.4)	239	94 (39.3)	239	164 (68.6)	<0.001
Previous MI	239	19 (8.0)	238	24 (10.1)	239	28 (11.7)	239	27 (11.3)	0.528
Previous PCI	239	45 (18.8)	238	52 (21.9)	239	54 (22.6)	239	41 (17.2)	0.406
Previous CABG	239	2 (0.8)	238	5 (2.1)	239	7 (2.9)	239	18 (7.5)	<0.001
Previous CAD (MI, PCI, or CABG)	239	48 (20.1)	238	58 (24.4)	239	63 (26.4)	239	57 (23.9)	0.436
Previous stroke	239	17 (7.1)	238	21 (8.8)	239	33 (13.8)	239	45 (18.8)	<0.001
Precious CHF hospitalization	239	11 (4.6)	238	18 (7.6)	239	23 (9.6)	239	61 (25.5)	<0.001
Previous cardiovascular events[#]	239	72 (30.1)	238	90 (37.8)	239	102 (42.7)	239	123 (51.5)	<0.001
Family history of cardiovascular events	239	72 (30.1)	238	66 (27.7)	239	65 (27.2)	239	55 (23.0)	0.365
Systolic blood pressure, mean (SD), mmHg	239	126 (16)	238	126 (17)	239	126 (17)	239	127 (21)	0.846
Diastolic blood pressure, mean (SD), mmHg	239	72 (12)	238	71 (13)	239	69 (12)	239	69 (13)	<0.001
Pulse rate, mean (SD), beats per minute	239	69 (12)	238	70 (12)	239	70 (17)	239	73 (14)	0.036
LDL-cholesterol, mean (SD), mg/dL	232	113 (31)	233	110 (29)	235	106 (33)	232	97 (33)	<0.001
HDL-cholesterol, mean (SD), mg/dL	232	62 (17)	233	58 (16)	231	56 (17)	229	54 (17)	<0.001
Triglycerides, median (IQR), mg/dL	233	115 (79-168)	235	110 (79-148)	235	100 (75-141)	235	94 (69-129)	0.001

Fasting glucose, median (IQR), mg/dL	239	106 (94-134)	231	108 (97-131)	234	109 (94-134)	234	112 (95-147)	0.811
Hemoglobin A1c, median (IQR), %	225	5.8 (5.5-6.3)	224	6.1 (5.6-6.9)	229	6.0 (5.6-7.0)	221	6.2 (5.7-7.1)	<0.001
Creatinine, median (IQR), mg/dL	239	0.7 (0.6-0.8)	238	0.7 (0.6-0.9)	239	0.8 (0.7-1.0)	239	1.0 (0.8-1.5)	<0.001
Hemoglobin, mean (SD), g/dL	239	13.5 (1.3)	236	13.0 (1.5)	239	12.7 (1.6)	238	11.4 (1.9)	<0.001
Hematocrit, mean (SD), %	239	40.2 (3.7)	236	39.0 (4.2)	239	38.0 (4.6)	237	34.6 (5.6)	<0.001
Uric acid, mean (SD), mg/dL	234	5.2 (1.5)	232	5.4 (1.5)	235	5.9 (1.6)	227	6.3 (1.9)	<0.001
NT-proBNP, median (IQR), pg/mL	239	98 (42-194)	238	140 (54-353)	239	252 (98-1039)	239	977 (253-3190)	<0.001
cTnI, median (IQR), pg/mL	239	0.0 (0.0-0.0)	238	0.0 (0.0-4.0)	239	0.0 (0.0-9.0)	239	9.0 (0.0-34.0)	<0.001
hs-CRP, median (IQR), mg/L	239	0.5 (0.2-1.3)	238	0.7 (0.3-2.0)	239	0.9 (0.3-3.2)	239	1.9 (0.5-5.4)	<0.001
GDF-15, median (IQR), pg/mL	239	647 (510-750)	238	1031 (932-1134)	239	1466 (1349-1652)	239	2823 (2249-4159)	<0.001
Anti-hypertensive drug use	239	178 (74.5)	238	191 (80.3)	239	200 (83.7)	239	210 (87.9)	0.002
RASI	239	117 (49.0)	238	124 (52.1)	239	145 (60.7)	239	168 (70.3)	<0.001
ACEI	239	26 (10.9)	238	28 (11.8)	239	38 (15.9)	239	43 (18.0)	0.081
ARB	239	94 (39.3)	238	100 (42.0)	239	111 (46.4)	239	135 (56.5)	<0.001
β-blocker	239	56 (23.4)	238	69 (29.0)	239	75 (31.4)	239	91 (38.1)	0.006
Any lipid-lowering drug use	239	129 (54.0)	238	137 (57.6)	239	147 (61.5)	239	124 (51.9)	0.157
Statin use	239	115 (48.1)	238	122 (51.3)	239	133 (55.7)	239	110 (46.0)	0.170
Any hypoglycemic drug use	239	51 (21.3)	238	65 (27.3)	239	67 (28.0)	239	90 (37.7)	0.001
Oral hypoglycemic drugs	239	43 (18.0)	238	55 (23.1)	239	54 (22.6)	239	71 (29.7)	0.025
Insulin	239	17 (7.1)	238	23 (9.7)	239	26 (10.9)	239	37 (15.5)	0.028
Any anti-platelet drug use	239	131 (54.8)	238	130 (54.6)	239	149 (62.3)	239	131 (54.8)	0.240
Aspirin use	239	127 (53.1)	238	111 (46.6)	239	129 (54.0)	239	121 (50.6)	0.376
Any anti-coagulant drugs	239	22 (9.2)	238	29 (12.2)	239	52 (21.8)	239	52 (21.8)	<0.001

Warfarin	239	19 (8.0)	238	22 (9.2)	239	41 (17.2)	239	46 (19.3)	<0.001
Incidence of events, no. (/1000 person-years)									
All-cause death	239	5 (7.1)	238	6 (8.6)	239	16 (22.8)	239	59 (93.8)	–
Cardiovascular death	239	0 (0.0)	238	2 (2.9)	239	4 (5.7)	239	18 (28.6)	–
Myocardial infarction	239	1 (1.4)	238	1 (1.4)	239	2 (2.9)	239	1 (1.6)	–
Stroke	239	6 (8.6)	238	5 (7.2)	239	3 (4.3)	239	10 (16.1)	–
First MACE**	239	7 (10.0)	238	7 (10.1)	239	8 (11.4)	239	28 (45.3)	–

Values are expressed as number (percentage) unless otherwise indicated. The quartiles of GDF-15 levels were as follows: quartile 1, ≤837.9; quartile 2, 838.1–1230.1; quartile 3, 1231.2–1927.2; quartile 4, ≥1928.1 pg/mL. GDF-15 indicates growth differentiation factor-15; SD, standard deviation; eGFR, estimated glomerular filtration rate; CAD, coronary artery disease; IQR, interquartile range; LMT, left main trunk; NYHA, New York Heart Association; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CHF, congestive heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; cTnI, contemporary sensitive cardiac troponin I; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; RASI, renin angiotensin system inhibitors; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; MACE, major adverse cardiovascular events.

*The *P* value is for comparison between groups, and is based on the χ^2 test of independence for categorical variables, and the analysis of variance or Kruskal-Wallis for continuous variables.

†Obesity is defined as a body mass index of 25 or more.

‡Chronic kidney disease is defined as an estimated GFR of less than 60 ml/min/1.73 m^2 of body surface area. eGFRs of stages 3a, 3b, 4, and 5 are defined as follows: stage 3a, 45–59 ml/min/1.73 m^2; stage 3b, 30–44 ml/min/1.73 m^2; stage 4, 15–29 ml/min/1.73 m^2; stage 5, ≤14 ml/min/1.73 m^2.

§The Gensini score represents the angiographic severity of coronary artery disease employing a nonlinear points system for degree of luminal narrowing.

‖Anemia is defined as a hemoglobin level of less than 13 g/dL in men and less than 12 g/dL in women.

#Previous cardiovascular events include myocardial infarction, stroke, heart failure hospitalization, and coronary revascularization.

**MACE is defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

Table S4. Baseline characteristics and incidence of outcomes according to quartiles of GDF-15 in former smokers.

Baseline characteristics and incidence of events	Quartile 1		Quartile 2		Quartile 3		Quartile 4		*P* value*
	No.	Value	No.	Value	No.	Value	No.	Value	
Baseline characteristics									
Age, mean (SD), y	258	65.5 (9.3)	259	71.6 (8.1)	259	74.4 (7.4)	259	75.7 (7.8)	<0.001
Male	258	215 (83.3)	259	229 (88.4)	259	217 (83.8)	259	229 (88.4)	0.165
Body mass index, mean (SD)	258	24.8 (3.4)	259	24.3 (3.5)	259	24.3 (3.8)	259	23.7 (3.6)	0.007
Obesity†	258	108 (41.9)	259	94 (36.3)	259	106 (40.9)	259	87 (33.6)	0.171
Hypertension	258	197 (76.4)	259	197 (76.1)	259	208 (80.3)	259	214 (82.6)	0.194
Dyslipidemia	258	177 (68.6)	259	173 (66.8)	259	163 (62.9)	259	142 (54.8)	0.006
Diabetes	258	101 (39.2)	259	129 (49.8)	259	116 (44.8)	259	146 (56.4)	<0.001
Current smoker	258	0 (0.0)	259	0 (0.0)	259	0 (0.0)	259	0 (0.0)	–
Former smoker	239	239 (100)	238	238 (100)	239	239 (100)	239	239 (100)	–
eGFR, mean (SD), ml/min/1.73 m^2	258	74.4 (17.8)	259	67.5 (16.4)	259	63.0 (15.8)	259	43.9 (23.5)	<0.001
Chronic kidney disease ‡	258	50 (19.4)	259	87 (33.6)	259	114 (44.0)	259	198 (76.5)	<0.001
Stage 3a		42 (16.3)		72 (27.8)		81 (31.3)		63 (24.3)	
Stage 3b		7 (2.7)		13 (5.0)		31 (12.0)		64 (24.7)	
Stage 4		0 (0.0)		1 (0.4)		2 (0.8)		34 (13.1)	
Stage 5		1 (0.4)		1 (0.4)		0 (0.0)		37 (14.3)	
Dialysis	258	0 (0)	259	1 (0.4)	259	0 (0.0)	259	35 (13.5)	<0.001
Gensini score, median (IQR)§	258	10.5 (2.5-31.9)	259	15.5 (5.0-38.5)	259	18.0 (4.5-43.5)	259	16.5 (5.0-52.0)	0.005
Obstructive CAD	258	145 (56.2)	259	168 (64.9)	259	172 (66.4)	259	171 (66.0)	0.051
Multi-vessel or LMT disease	258	83 (32.2)	259	86 (33.2)	259	96 (37.1)	259	108 (41.7)	0.098

NYHA class III or IV	258	10 (3.9)	259	14 (5.4)	259	20 (7.7)	259	44 (17.0)	<0.001
Atrial fibrillation	258	15 (5.8)	259	23 (8.9)	259	24 (9.3)	259	42 (16.2)	<0.001
Malignancies	258	18 (7.0)	259	28 (10.8)	259	34 (13.1)	259	42 (16.2)	0.010
Anemia[||]	258	18 (7.0)	259	28 (10.8)	259	34 (13.1)	259	42 (16.2)	0.010
Previous MI	258	51 (19.8)	259	51 (19.7)	259	37 (14.3)	259	56 (21.6)	0.165
Previous PCI	258	80 (31.0)	259	84 (32.4)	259	78 (30.1)	259	79 (30.5)	0.946
Previous CABG	258	8 (3.1)	259	9 (3.5)	259	14 (5.4)	259	18 (7.0)	0.138
Previous CAD (MI, PCI, or CABG)	258	88 (34.1)	259	92 (35.5)	259	91 (35.1)	259	98 (37.8)	0.840
Previous stroke	258	27 (10.5)	259	47 (18.2)	259	46 (17.8)	259	53 (20.5)	0.015
Precious CHF hospitalization	258	7 (2.7)	259	16 (6.2)	259	23 (8.9)	259	58 (22.4)	<0.001
Previous cardiovascular events[#]	258	113 (43.8)	259	136 (52.5)	259	134 (51.7)	259	155 (59.9)	0.004
Family history of cardiovascular events	258	87 (33.7)	259	85 (32.8)	259	84 (32.4)	259	64 (24.7)	0.096
Systolic blood pressure, mean (SD), mmHg	258	129 (18)	259	126 (17)	259	128 (19)	259	127 (19)	0.455
Diastolic blood pressure, mean (SD), mmHg	258	73 (11)	259	69 (12)	259	70 (12)	259	69 (12)	<0.001
Pulse rate, mean (SD), beats per minute	258	68 (11)	259	69 (12)	259	71 (13)	259	73 (14)	<0.001
LDL-cholesterol, mean (SD), mg/dL	247	109 (30)	254	104 (26)	257	102 (29)	255	93 (27)	<0.001
HDL-cholesterol, mean (SD), mg/dL	253	53 (15)	254	54 (17)	249	55 (15)	254	51 (15)	0.012
Triglycerides, median (IQR), mg/dL	253	127 (91-199)	255	115 (84-171)	255	115 (81-153)	256	102 (75-144)	<0.001
Fasting glucose, median (IQR), mg/dL	253	107 (96-130)	257	116 (97-154)	258	114 (100-147)	256	112 (95-155)	0.012

Hemoglobin A1c, median (IQR), %	244	5.9 (5.6-6.8)	248	6.2 (5.7-7.3)	250	6.1 (5.7-7.1)	247	6.2 (5.7-7.3)	0.047
Creatinine, median (IQR), mg/dL	258	0.8 (0.7-0.9)	259	0.9 (0.7-1.0)	259	0.9 (0.8-1.0)	259	1.2 (0.9-1.8)	<0.001
Hemoglobin, mean (SD), g/dL	257	13.9 (1.3)	258	13.6 (1.5)	259	13.2 (1.6)	259	11.9 (2.0)	<0.001
Hematocrit, mean (SD), %	257	41.3 (3.9)	258	40.7 (4.2)	259	39.6 (4.6)	259	35.9 (6.0)	<0.001
Uric acid, mean (SD), mg/dL	250	6.0 (1.5)	253	5.8 (1.4)	253	6.1 (1.7)	248	6.3 (1.9)	0.003
NT-proBNP, median (IQR), pg/mL	258	87 (40-213)	259	148 (61-394)	259	188 (77-653)	259	732 (217-2436)	<0.001
cTnI, median (IQR), pg/mL	258	0.0 (0.0-1.0)	259	0.0 (0.0-7.0)	259	0.0 (0.0-10.0)	259	8.0 (0.0-33.0)	<0.001
hs-CRP, median (IQR), mg/L	258	0.5 (0.2-1.7)	259	0.6 (0.3-2.0)	259	1.0 (0.4-3.2)	259	1.5 (0.4-5.7)	<0.001
GDF-15, median (IQR), pg/mL	258	739 (608-856)	259	1172 (1069-1274)	259	1617 (1512-1765)	259	2747 (2200-4084)	<0.001
Anti-hypertensive drug use	258	203 (78.7)	259	204 (78.8)	259	209 (80.7)	259	222 (85.7)	0.139
RASI	258	136 (52.7)	259	156 (60.2)	259	162 (62.6)	259	172 (66.4)	0.013
ACEI	258	39 (15.1)	259	38 (14.7)	259	35 (13.5)	259	64 (24.7)	0.002
ARB	258	99 (38.4)	259	124 (47.9)	259	127 (49.0)	259	124 (47.9)	0.052
β-blocker	258	73 (28.3)	259	73 (28.2)	259	65 (25.1)	259	86 (33.2)	0.234
Any lipid-lowering drug use	258	158 (61.2)	259	157 (60.6)	259	155 (59.9)	259	140 (54.1)	0.320
Statin use	258	145 (56.2)	259	141 (54.4)	259	128 (49.4)	259	117 (45.2)	0.051
Any hypoglycemic drug use	258	74 (28.7)	259	92 (35.5)	259	85 (32.8)	259	91 (35.1)	0.327
Oral hypoglycemic drugs	258	67 (26.0)	259	75 (29.0)	259	68 (26.3)	259	62 (23.9)	0.636
Insulin	258	16 (6.2)	259	31 (12.0)	259	33 (12.7)	259	44 (17.0)	0.002
Any anti-platelet drug use	258	177 (68.6)	259	189 (73.0)	259	172 (66.4)	259	168 (64.9)	0.217
Aspirin use	258	163 (63.2)	259	171 (66.0)	259	150 (57.9)	259	140 (54.1)	0.026
Any anti-coagulant drugs	258	24 (9.3)	259	39 (15.1)	259	44 (17.0)	259	59 (22.8)	<0.001
Warfarin	258	18 (7.0)	259	35 (13.5)	259	39 (15.1)	259	55 (21.2)	<0.001

Incidence of events, no. (/1000 person-years)									
All-cause death	258	7 (9.3)	259	13 (17.1)	259	24 (32.0)	259	76 (116.2)	–
Cardiovascular death	258	2 (2.7)	259	6 (7.9)	259	7 (9.3)	259	32 (48.9)	–
Myocardial infarction	258	1 (1.3)	259	1 (1.3)	259	2 (2.7)	259	6 (9.2)	–
Stroke	258	5 (6.7)	259	10 (13.6)	259	6 (8.1)	259	10 (15.5)	–
First MACE**	258	8 (10.7)	259	16 (21.8)	259	14 (18.9)	259	42 (65.5)	–

Values are expressed as number (percentage) unless otherwise indicated. The quartiles of GDF-15 levels were as follows: quartile 1, ≤973.0; quartile 2, 982.6–1371.3; quartile 3, 1373.0–1980.2; quartile 4, ≥1980.9 pg/mL. GDF-15 indicates growth differentiation factor-15; SD, standard deviation; eGFR, estimated glomerular filtration rate; CAD, coronary artery disease; IQR, interquartile range; LMT, left main trunk; NYHA, New York Heart Association; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CHF, congestive heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; cTnI, contemporary sensitive cardiac troponin I; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; RASI, renin angiotensin system inhibitors; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; MACE, major adverse cardiovascular events.

*The *P* value is for comparison between groups, and is based on the χ^2 test of independence for categorical variables, and the analysis of variance or Kruskal-Wallis for continuous variables.

†Obesity is defined as a body mass index of 25 or more.

‡Chronic kidney disease is defined as an estimated GFR of less than 60 ml/min/1.73 m^2 of body surface area. eGFRs of stages 3a, 3b, 4, and 5 are defined as follows: stage 3a, 45–59 ml/min/1.73 m^2; stage 3b, 30–44 ml/min/1.73 m^2; stage 4, 15–29 ml/min/1.73 m^2; stage 5, ≤14 ml/min/1.73 m^2.

§The Gensini score represents the angiographic severity of coronary artery disease employing a nonlinear points system for degree of luminal narrowing.

‖Anemia is defined as a hemoglobin level of less than 13 g/dL in men and less than 12 g/dL in women.

#Previous cardiovascular events include myocardial infarction, stroke, heart failure hospitalization, and coronary revascularization.

**MACE is defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

Table S5. Baseline characteristics and incidence of outcomes according to quartiles of GDF-15 in current smokers.

Baseline characteristics and incidence of events	Quartile 1		Quartile 2		Quartile 3		Quartile 4		*P* value*
	No.	Value	No.	Value	No.	Value	No.	Value	
Baseline characteristics									
Age, mean (SD), y	107	56.6 (12.1)	107	65.4 (9.3)	107	69.8 (9.2)	107	70.3 (9.1)	<0.001
Male	107	92 (86.0)	107	89 (83.2)	107	91 (85.1)	107	91 (85.1)	0.951
Body mass index, mean (SD)	107	25.1 (4.0)	107	25.1 (3.9)	107	24.4 (4.2)	107	22.9 (3.7)	<0.001
Obesity†	107	50 (46.7)	107	54 (50.5)	107	40 (37.4)	107	32 (29.9)	0.010
Hypertension	107	68 (63.6)	107	86 (80.4)	107	81 (75.7)	107	88 (82.2)	0.007
Dyslipidemia	107	72 (67.3)	107	61 (57.0)	107	56 (52.3)	107	59 (55.1)	0.133
Diabetes	107	40 (37.4)	107	45 (42.1)	107	57 (53.3)	107	64 (59.8)	0.004
Current smoker	107	107 (100.0)	107	107 (100.0)	107	107 (100.0)	107	107 (100.0)	–
Former smoker	107	0 (0.0)	107	0 (0.0)	107	0 (0.0)	107	0 (0.0)	–
eGFR, mean (SD), ml/min/1.73 m^2	107	80.5 (20.2)	107	73.9 (17.4)	107	62.1 (16.2)	107	51.1 (25.7)	<0.001
Chronic kidney disease ‡	107	10 (9.4)	107	21 (19.6)	107	54 (50.5)	107	68 (63.6)	<0.001
Stages of chronic kidney disease	107		107		107		107		<0.001
Stage 3a		7 (6.5)		20 (18.7)		38 (35.5)		31 (29.0)	
Stage 3b		3 (2.8)		1 (0.9)		15 (14.0)		14 (13.1)	
Stage 4		0 (0.0)		0 (0.0)		1 (0.9)		10 (9.4)	
Stage 5		0 (0.0)		0 (0.0)		0 (0.0)		13 (12.2)	
Dialysis	107	0 (0.0)	107	0 (0.0)	107	0 (0.0)	107	13 (12.2)	<0.001
Gensini score, median (IQR)§	107	8.0 (0.0-31.0)	107	10.0 (2.0-34.0)	107	15.5 (3.5-39.0)	107	18.0 (2.5-49.0)	0.050
Obstructive CAD	107	55 (51.4)	107	56 (52.3)	107	67 (62.6)	107	68 (63.6)	0.136

Multi-vessel or LMT disease	107	30 (28.0)	107	33 (30.8)	107	42 (39.3)	107	52 (48.6)	0.008
NYHA class III or IV	107	5 (4.7)	107	9 (8.4)	107	10 (9.4)	107	27 (25.2)	<0.001
Atrial fibrillation	107	7 (6.5)	107	8 (7.5)	107	9 (8.4)	107	16 (15.0)	0.138
Malignancies	107	5 (4.7)	107	7 (6.5)	107	11 (10.3)	107	13 (12.2)	0.183
Anemia[ll]	107	15 (14.0)	107	21 (19.6)	107	34 (31.8)	107	69 (64.5)	<0.001
Previous MI	107	12 (11.2)	107	21 (19.6)	107	12 (11.2)	107	16 (15.0)	0.242
Previous PCI	107	18 (16.8)	107	29 (27.1)	107	27 (25.2)	107	22 (20.6)	0.264
Previous CABG	107	2 (1.9)	107	0 (0.0)	107	2 (1.9)	107	4 (3.7)	0.253
Previous CAD (MI, PCI, or CABG)	107	20 (18.7)	107	31 (29.0)	107	27 (25.2)	107	28 (26.2)	0.353
Previous stroke	107	11 (10.3)	107	18 (16.8)	107	19 (17.8)	107	16 (15.0)	0.425
Precious CHF hospitalization	107	5 (4.7)	107	7 (6.5)	107	9 (8.4)	107	15 (14.0)	0.079
Previous cardiovascular events[#]	107	36 (33.6)	107	45 (42.1)	107	48 (44.9)	107	44 (41.1)	0.383
Family history of cardiovascular events	107	39 (36.5)	107	28 (26.2)	107	23 (21.5)	107	23 (21.5)	0.042
Systolic blood pressure, mean (SD), mmHg	107	126 (18)	107	130 (19)	107	125 (17)	107	124 (19)	0.100
Diastolic blood pressure, mean (SD), mmHg	107	74 (14)	107	73 (14)	107	70 (11)	107	68 (12)	0.001
Pulse rate, mean (SD), beats per minute	107	69 (12)	107	69 (13)	107	71 (14)	107	73 (13)	0.058
LDL-cholesterol, mean (SD), mg/dL	103	115 (35)	104	107 (29)	107	107 (31)	107	99 (31)	0.003
HDL-cholesterol, mean (SD), mg/dL	104	50 (15)	103	52 (14)	106	51 (16)	105	48 (15)	0.387
Triglycerides, median (IQR), mg/dL	106	162 (103-236)	105	128 (102-182)	107	110 (83-177)	107	113 (84-165)	<0.001

Fasting glucose, median (IQR), mg/dL	103	107 (95-143)	106	115 (97-152)	106	113 (95-142)	104	116 (94-165)	0.500
Hemoglobin A1c, median (IQR), %	103	5.9 (5.6-6.8)	105	6.1 (5.5-7.2)	106	6.4 (5.7-7.2)	104	6.4 (5.7-7.1)	0.145
Creatinine, median (IQR), mg/dL	107	0.8 (0.7-0.9)	107	0.8 (0.7-0.9)	107	0.9 (0.8-1.1)	107	1.1 (0.8-1.4)	<0.001
Hemoglobin, mean (SD), g/dL	107	14.6 (1.7)	106	14.0 (1.5)	107	13.4 (1.7)	107	12.0 (2.1)	<0.001
Hematocrit, mean (SD), %	107	43.6 (4.9)	106	41.7 (4.5)	107	40.3 (5.0)	107	36.2 (6.3)	<0.001
Uric acid, mean (SD), mg/dL	105	6.0 (1.7)	103	5.8 (1.6)	103	6.3 (1.7)	104	6.7 (2.0)	0.001
NT-proBNP, median (IQR), pg/mL	107	96 (38-423)	107	160 (53-460)	107	217 (87-727)	107	988 (245-2740)	<0.001
cTnI, median (IQR), pg/mL	107	0.0 (0.0-8.0)	107	0.0 (0.0-11.0)	107	0.0 (0.0-13.0)	107	10.0 (0.0-37.0)	<0.001
hs-CRP, median (IQR), mg/L	107	1.0 (0.4-2.4)	107	1.2 (0.4-4.6)	107	1.5 (0.4-5.7)	107	3.5 (0.9-8.0)	<0.001
GDF-15, median (IQR), pg/mL	107	689 (529-819)	107	1116 (1038-1255)	107	1659 (1480-1819)	107	2767 (2327-4257)	<0.001
Anti-hypertensive drug use	107	78 (72.9)	107	91 (85.1)	107	82 (76.6)	107	99 (92.5)	<0.001
RASI	107	52 (48.6)	107	63 (58.9)	107	63 (58.9)	107	74 (69.2)	0.025
ACEI	107	11 (10.3)	107	24 (22.4)	107	17 (15.9)	107	25 (23.4)	0.043
ARB	107	41 (38.3)	107	41 (38.3)	107	49 (45.8)	107	58 (54.2)	0.059
β-blocker	107	30 (28.0)	107	29 (27.1)	107	30 (28.0)	107	38 (35.5)	0.501
Any lipid-lowering drug use	107	56 (52.3)	107	62 (57.9)	107	56 (52.3)	107	61 (57.0)	0.762
Statin use	107	50 (46.7)	107	56 (52.3)	107	54 (50.5)	107	51 (47.7)	0.837
Any hypoglycemic drug use	107	25 (23.4)	107	33 (30.8)	107	42 (39.3)	107	45 (42.1)	0.016
Oral hypoglycemic drugs	107	19 (17.8)	107	24 (22.4)	107	35 (32.7)	107	30 (28.0)	0.065
Insulin	107	10 (9.4)	107	15 (14.0)	107	11 (10.3)	107	22 (20.6)	0.069
Any anti-platelet drug use	107	63 (58.9)	107	72 (67.3)	107	62 (57.9)	107	65 (60.8)	0.493
Aspirin use	107	59 (55.1)	107	65 (60.8)	107	50 (46.7)	107	54 (50.5)	0.193
Any anti-coagulant drugs	107	12 (11.2)	107	9 (8.4)	107	13 (12.2)	107	28 (26.2)	0.001

Warfarin	107	10 (9.4)	107	9 (8.4)	107	12 (11.2)	107	26 (24.3)	0.002
Incidence of events, no. (/1000 person-years)									
All-cause death	107	6 (19.3)	107	4 (12.7)	107	10 (32.8)	107	28 (98.9)	–
Cardiovascular death	107	2 (6.4)	107	2 (6.3)	107	1 (3.3)	107	12 (42.4)	–
Myocardial infarction	107	1 (3.2)	107	1 (3.2)	107	2 (6.6)	107	2 (7.1)	–
Stroke	107	5 (16.4)	107	3 (9.6)	107	2 (6.6)	107	4 (14.3)	–
First MACE**	107	8 (26.3)	107	6 (19.3)	107	5 (16.6)	107	16 (57.9)	–

Values are expressed as number (percentage) unless otherwise indicated. The quartiles of GDF-15 levels were as follows: quartile 1, ≤927.0; quartile 2, 928.0–1368.7; quartile 3, 1371.9–2087.3; quartile 4, ≥2098.6 pg/mL. GDF-15 indicates growth differentiation factor-15; SD, standard deviation; eGFR, estimated glomerular filtration rate; CAD, coronary artery disease; IQR, interquartile range; LMT, left main trunk; NYHA, New York Heart Association; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CHF, congestive heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; cTnI, contemporary sensitive cardiac troponin I; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; RASI, renin angiotensin system inhibitors; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; MACE, major adverse cardiovascular events.

*The *P* value is for comparison between groups, and is based on the χ^2 test of independence for categorical variables, and the analysis of variance or Kruskal-Wallis for continuous variables.

†Obesity is defined as a body mass index of 25 or more.

‡Chronic kidney disease is defined as an estimated GFR of less than 60 ml/min/1.73 m^2 of body surface area. eGFRs of stages 3a, 3b, 4, and 5 are defined as follows: stage 3a, 45–59 ml/min/1.73 m^2; stage 3b, 30–44 ml/min/1.73 m^2; stage 4, 15–29 ml/min/1.73 m^2; stage 5, ≤14 ml/min/1.73 m^2.

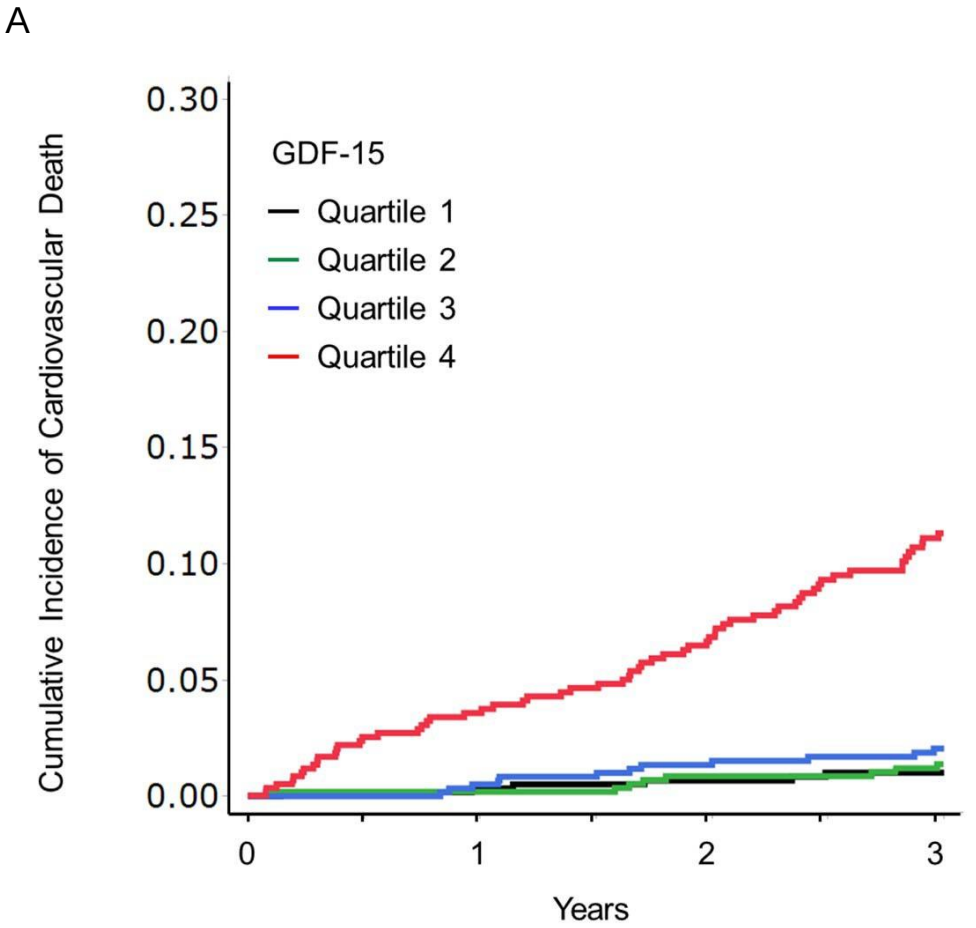
§The Gensini score represents the angiographic severity of coronary artery disease employing a nonlinear points system for degree of luminal narrowing.

‖Anemia is defined as a hemoglobin level of less than 13 g/dL in men and less than 12 g/dL in women.

#Previous cardiovascular events include myocardial infarction, stroke, heart failure hospitalization, and coronary revascularization.

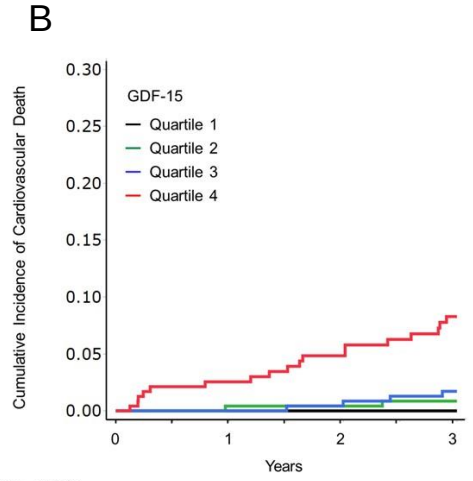
**MACE is defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

Figure S1. Cumulative incidence of cardiovascular death in the entire cohort (A), never smokers (B), former smokers (C), and current smokers (D) according to the serum GDF-15 level at baseline. Follow-up results are truncated after 3 years. GDF-15 indicates growth differentiation factor 15.



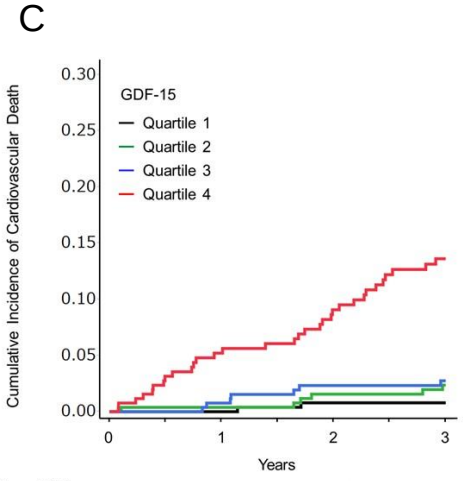
No. at Risk

Quartile 1	605	601	596	592	590	581	577
Quartile 2	604	600	599	594	588	586	578
Quartile 3	604	601	596	588	574	564	551
Quartile 4	605	571	544	528	503	468	440



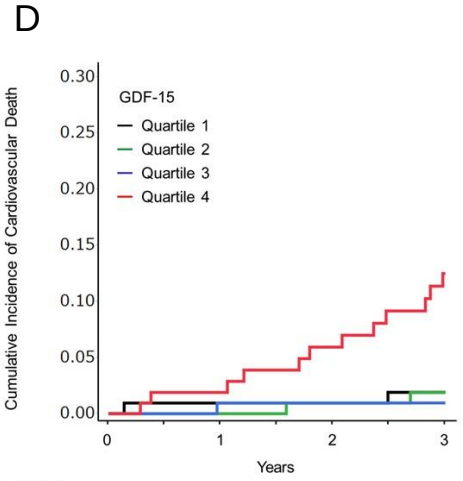
No. at Risk

Quartile 1	239	239	238	237	237	233	231
Quartile 2	238	237	236	234	232	230	229
Quartile 3	239	237	237	236	232	230	223
Quartile 4	239	227	220	210	202	191	180



No. at Risk

Quartile 1	258	256	254	251	250	247	246
Quartile 2	259	257	256	254	250	248	246
Quartile 3	259	259	257	252	246	239	233
Quartile 4	259	241	224	220	208	192	180

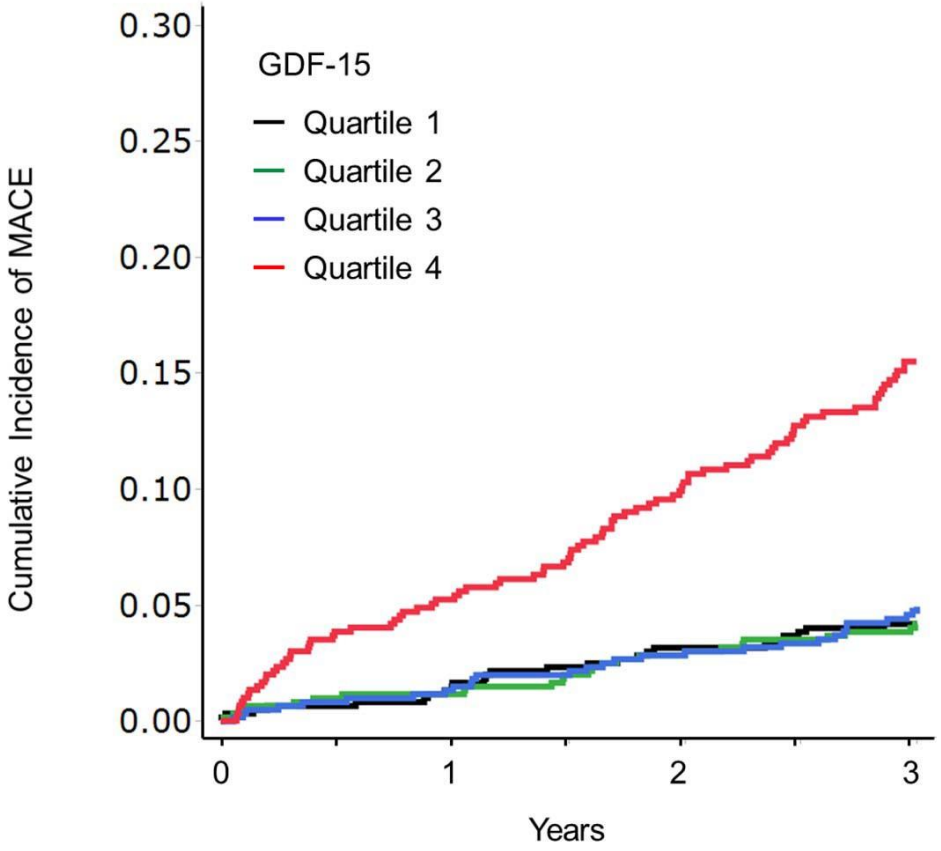


No. at Risk

Quartile 1	107	105	104	104	103	102	101
Quartile 2	107	106	106	106	105	105	102
Quartile 3	107	106	103	102	99	99	97
Quartile 4	107	103	100	96	91	83	78

Figure S2. Cumulative incidence of MACE in the entire cohort (A), never smokers (B), former smokers (C), and current smokers (D) according to the serum GDF-15 level at baseline. Follow-up results are truncated after 3 years. MACE indicates major adverse cardiovascular events; and GDF-15, growth differentiation factor 15.

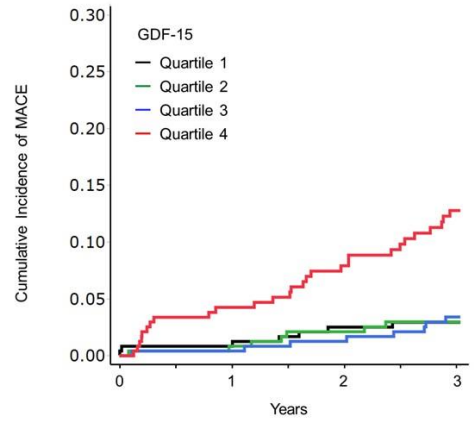
A



No. at Risk

Quartile 1	605	598	589	582	576	566	560
Quartile 2	604	595	593	583	576	570	562
Quartile 3	604	597	592	582	566	555	538
Quartile 4	605	565	537	518	488	455	424

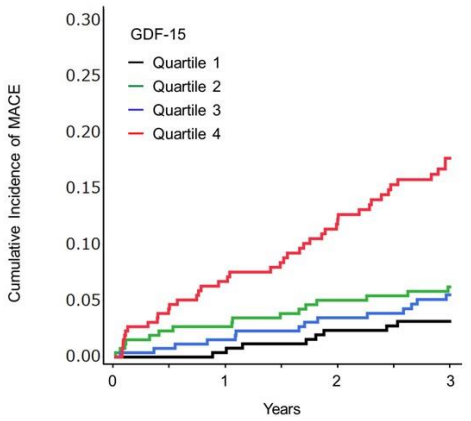
B



No. at Risk

Quartile 1	239	237	235	233	231	227	225
Quartile 2	238	236	235	230	228	225	225
Quartile 3	239	237	237	235	231	229	220
Quartile 4	239	225	217	207	197	186	174

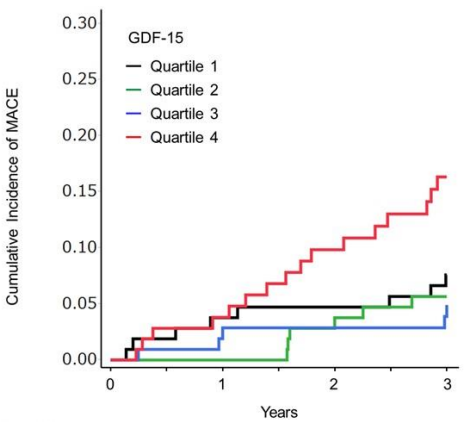
C



No. at Risk

Quartile 1	258	256	252	249	246	242	240
Quartile 2	259	252	250	245	241	238	236
Quartile 3	259	257	255	250	243	235	228
Quartile 4	259	238	222	216	201	187	173

D



No. at Risk

Quartile 1	107	104	102	101	100	99	96
Quartile 2	107	106	106	106	103	101	98
Quartile 3	107	105	102	100	97	97	94
Quartile 4	107	102	98	93	88	80	75

Figure S3. Adjusted hazard ratios of the quartiles of GDF-15 levels for all-cause death in the entire cohort, never smokers, former smokers, and current smokers. The data were adjusted for age, sex, body mass index, hypertension, dyslipidemia, diabetes, and current smoking, eGFR, the Gensini score, previous myocardial infarction, previous stroke, previous heart failure hospitalization, malignancies, anemia, antihypertensive drug use, statin use, and cardiovascular biomarkers (NT-proBNP, cTnI, and hs-CRP). The biomarkers were modeled as continuous variables. CI indicates confidence interval; HR, hazard ratio; GDF-15, growth differentiation factor 15; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; cTnI, contemporary sensitive cardiac troponin I; and hs-CRP, high-sensitivity C-reactive protein.

Subgroups	HR	95% CI Lower	95% CI Upper	*P*-Value
Entire cohort				
Quartile 1	reference			
Quartile 2	0.72	0.39	1.34	
Quartile 3	1.28	0.75	2.25	
Quartile 4	3.13	1.86	5.51	<0.001
Never smokers				
Quartile 1	reference			
Quartile 2	0.91	0.27	3.22	
Quartile 3	2.14	0.79	6.85	
Quartile 4	5.76	2.17	18.3	<0.001
Former smokers				
Quartile 1	reference			
Quartile 2	1.15	0.46	3.11	
Quartile 3	1.72	0.75	4.46	
Quartile 4	4.48	1.97	11.6	<0.001
Current smokers				
Quartile 1	reference			
Quartile 2	0.29	0.07	1.06	
Quartile 3	0.52	0.17	1.66	
Quartile 4	1.10	0.38	3.52	0.06