ESM Methods

Statistical analysis

Data are presented as mean (SD) or as a percentage. For variables with skewed distribution, data are presented as median (interquartile range [IQR]) and were analysed after log_e-transformation. Comparison of clinical characteristics between two independent groups was performed by Chi square test for categorical variables, and t-test or Mann-Whitney U test for continuous variables, where appropriate. The association of different cardiovascular risk factors with FGF21 levels at baseline was assessed using univariable and multivariable linear regression analysis with FGF21 modeled as the dependent variable. No multi-collinearity issue was detected in multivariable linear regression models as assessed by the variance inflation factor (< 5.0).

Cox regression was used to compute HR and its 95% CIs to assess the association of FGF21 levels at baseline with different outcome events. The proportional hazard assumptions were checked using Schoenfeld residuals and no significant deviation from the assumptions was found for all the outcomes. To investigate the assumption of linearity of the relationship between log_e-transformed FGF21 levels and outcomes, log_e-transformed FGF21 levels were categorised using deciles and plots of the log_e HR (obtained from Cox models including log_e-transformed FGF21 decile variable and treatment allocation) versus the median of the category were constructed. Also tests for deviation from linearity were conducted by fitting models including both a linear and a categorical version (decile) of the variable-grouped log_e-transformed FGF21 levels, and treatment allocation. For this method, the test of the overall effect of the individual categories assessed the significance of a non-linear component [1]. These tests indicated a significant deviation from linearity for the

outcome of coronary and carotid revascularisation ($p = 0.02$), but not for other outcomes. Therefore, tertiles of baseline FGF21 levels were used as the main analysis but results based on the association of $\log_e$-transformed FGF21 levels with outcomes were also shown in a separate analysis except for coronary and carotid revascularisation. Model 1 included treatment allocation. Model 2 further adjusted for traditional cardiovascular risk factors, including age, sex, known diabetes duration, prior history of CVD, smoking (never, former and current), BMI, HbA_{1c}, HOMA-IR, systolic BP, HDL cholesterol, LDL cholesterol, triacylglycerol, fibrinogen, plasma creatinine and homocysteine at baseline. Replacement of plasma creatinine by estimated GFR in all the Cox regression models made little difference to results (data not shown). The p values for interaction were estimated by including the multiplicative interaction term in the regression models in the full sample after adjusting for the main effects of the covariates.

The incremental value of the addition of $\log_e$-transformed FGF21 levels in the risk prediction model was assessed by the change in Harrell's C-statistic using a method adapted for survival models [2]. Integrated discrimination improvement (IDI) and net reclassification improvement (NRI) were also assessed as described previously [3]. The goodness of fit of the models was assessed using the Gronnesby and Borgan test [4]. As the NRI method is highly sensitive to the chosen cut-points of risk and there are no pre-specified cut-points that can be applied to all different outcomes appropriately, the category-free NRI (NRI >0) approach was utilised with both "event NRI" and "nonevent NRI" calculated [5]. IDI and NRI were analysed using the packages "survIDINRI" and "nricens" respectively in R platform for statistical computing version 3.1.0.

References

1. Pasta D (2009) Learning when to be discrete: continuous vs. categorical predictors. SAS Glob Forum Pap 248:1–10

2. Newson RB (2011) Comparing the predictive powers of survival models using Harrell's C or Somers' D. Stata J 10:339-358

3. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS (2008) Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 27:157-172

4. May S, Hosmer DW (1998) A simplified method of calculating an overall goodness-of-fit test for the Cox proportional hazards model. Lifetime Data Anal 4:109-120

5. Pencina MJ, D'Agostino RB Sr, Steyerberg EW (2011) Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Stat Med 30:11-21

ESM Table 1 Baseline characteristics of the patients with and without valid data on FGF21 levels

Characteristics	With (*n=9,697*)	Without (*n=98*)	*p* value[a]
Age (years)	62.2 ± 6.9	62.1 ± 6.7	0.80
Male	6,078 (62.7)	60 (61.2)	0.77
BMI (kg/m^2)	29.8 (26.8-33.5)	30.7 (27.1-33.5)	0.40
Waist-to-hip ratio	0.94 (0.88-0.98)	0.94 (0.89-0.98)	0.80
Known diabetes duration (years)	5 (2-10)	6 (3-10)	0.33
Prior history of CVD	2,102 (21.7)	29 (29.6)	0.06

Data are expressed as mean ± SD, *n* (%) or median (IQR).

[a]*P* values were calculated by t-test, chi-square test or Mann-Whitney U test, where appropriate.

ESM Table 2 Plasma FGF21 levels at baseline and one year, and analysis of relative change in a random sub-sample of 1,919 patients

FGF21 levels	All (*n*=1,919)	Men (*n*=1,197)	Women (*n*=722)	*p* value for sex difference
Levels, pg/ml, median (IQR)				
Baseline (*n*=1,919)	317 (206-497)	293 (194-450)	367 (229-569)	<0.001
One-year				
Placebo (*n*=963)	342 (223-536)	318 (213-515)	382 (242-595)	<0.001
Fenofibrate (*n*=956)	647 (415-1017)	599 (387-948)	723 (485-1195)	0.001
Relative change, % (95% CI)				
Placebo (*n*=963)	11.2 (7.8, 14.7)*	12.3 (7.8, 17.1)*	9.6 (4.6, 14.7)*	0.44
Fenofibrate (*n*=956)	101.5 (93.6, 109.6)*	103.5 (93.6, 113.8)*	97.8 (85.1, 111.3)*	0.51
Treatment effect, % (95% CI)	81.2 (72.3, 90.5)	81.1 (69.6, 93.3)	80.5 (66.8, 95.3)	0.95
p value for treatment effect	<0.001	<0.001	<0.001	

The *p* values for sex and treatment difference were estimated by t-test after $\log_e$-transformation

*$p<0.001$ compared to baseline using paired t-test after $\log_e$-transformation.

ESM Table 3 Association of different CVD risk factors with FGF21 levels at baseline using univariable and multivariable linear regression analysis with $\log_e$-transformed FGF21 levels as the dependent variable

Parameter	Univariable analysis		Multivariable analysis[a]	
	% change (95% CI)	*p* value	% change (95% CI)	*p* value
Age (years)	0.6 (0.4, 0.8)	<0.001	1.0 (0.8, 1.3)	<0.001
Male	-15.5 (-17.9, -13.0)	<0.001	-21.9 (-25.2, -18.4)	<0.001
White	4.9 (-1.4, 11.5)	0.13	-0.3 (-6.1, 5.8)	0.91
Current smoker	13.3 (8.0, 18.9)	<0.001	23.4 (17.3, 29.8)	<0.001
Ex-smoker	4.1 (1.3, 7.1)	0.005	7.6 (4.4, 10.9)	<0.001
Prior history of CVD	14.3 (10.5, 18.3)	<0.001	6.7 (3.1, 10.4)	<0.001
Known diabetes duration (years)[b]	-2.2 (-3.8, -0.6)	0.007	-2.9 (-4.4, -1.2)	<0.001
BMI (kg/m^2)[b]	143.7 (125.2, 163.8)	<0.001	58.6 (43.7, 75.0)	<0.001
Waist-to-hip ratio[b]	64.9 (39.4, 95.0)	<0.001	66.1 (34.5, 105.1)	<0.001
Fasting insulin (pmol/l)[b]	27.2 (24.6, 29.8)	<0.001	-	-
Fasting glucose (mmol/l)[b]	16.2 (10.5, 22.2)	<0.001	24.9 (15.5, 35.1)	<0.001
HOMA-IR[b]	35.1 (32.0, 38.2)	<0.001	16.2 (13.0, 19.4)	<0.001
HbA$_{1c}$ (%)[b,c]	9.9 (1.8, 18.5)	0.02	-24.8 (-33.2, -15.2)	<0.001
Systolic BP (mmHg)	0.3 (0.2, 0.4)	<0.001	0.0 (-0.1, 0.1)	0.80
Diastolic BP (mmHg)	0.3 (0.2, 0.5)	<0.001	0.0 (-0.2, 0.2)	0.90
Total cholesterol (mmol/l)	2.1 (0.1, 4.1)	0.04	-	-
HDL cholesterol (mmol/l)	-20.5 (-24.7, -16.1)	<0.001	-2.0 (-12.5, 9.6)	0.72
LDL cholesterol (mmol/l)	-10.1 (-12.0, -8.2)	<0.001	-4.1 (-6.1, -2.0)	<0.001
Triacylglycerol (mmol/l)[b]	64.9 (59.5, 70.5)	<0.001	46.0 (40.2, 52.1)	<0.001
Apolipoprotein A-I (g/l)	-3.0 (-9.3, 3.7)	0.38	10.2 (-3.5, 26.0)	0.15
Apolipoprotein A-II (g/l)	21.8 (-0.2, 48.6)	0.05	1.9 (-19.6, 29.1)	0.88
Apolipoprotein B (g/l)	40.8 (29.8, 52.6)	<0.001	-	-
Fibrinogen (g/l)	1.5 (-0.4, 3.4)	0.11	-3.8 (-5.6, -1.9)	<0.001
Plasma creatinine (μmol/l)	0.2 (0.1, 0.3)	<0.001	0.3 (0.2, 0.4)	<0.001
Homocysteine (μmol/l)[b]	35.5 (29.2, 42.1)	<0.001	28.2 (21.7, 35.1)	<0.001
Estimated GFR (ml min^{-1} 1.73 m^{-2})	-0.4 (-0.5, -0.3)	<0.001	-	-

The percentage change was estimated by the exponentiation of coefficients from linear regression analysis.

[a]All variables were entered into the multivariable model except fasting insulin, total cholesterol, apolipoprotein B and estimated GFR due to multi-collinearity issues with HOMA-IR, LDL cholesterol and plasma creatinine. The variance inflation factors of all the predictor variables in the multivariable model are <5.0.

[b]Data were $\log_e$-transformed before analysis.

[c]When HbA$_{1c}$ was expressed in the unit of mmol/mol, the percentage change (95% CI) per one unit change in loge-transformed value was 7.1% (95% CI 1.6, 12.8) in univariable analysis and -17.0% (95% CI -23.5, -10.0) in multivariable analysis.

ESM Table 4 Association of the use of different concomitant glucose-lowering medication with FGF21 levels at baseline using linear regression analysis with $\log_e$-transformed FGF21 levels as the dependent variable

Treatment	n	FGF21 levels (pg/ml)	Age- and sex-adjusted linear regression model		Multivariable linear regression model[a]	
			Coefficient (SE)	p value	Coefficient (SE)	p value
Diet alone	2,584	299 (199-456)	referent	-	referent	-
Oral agent alone	5,780	327 (216-501)	0.091 (0.016)	<0.001	0.047 (0.018)	0.009
Insulin alone	600	267 (165-426)	-0.142 (0.031)	<0.001	-0.153 (0.034)	<0.001
Insulin + oral agent	733	320 (194-485)	0.049 (0.029)	0.091	-0.089 (0.032)	0.006
Overall effect p				0.008		<0.001

FGF21 levels are expressed as median (IQR) and $\log_e$-transformed before analysis.

[a]Adjusted for all the significant variables in the multivariable analysis in ESM Table 3.

ESM Table 5 Association of the use of different concomitant cardiovascular medication with FGF21 levels at baseline using linear regression analysis with $\log_e$-transformed FGF21 levels as the dependent variable

Medication	Without drug treatment		With drug treatment		Age- and sex-adjusted linear regression model		Multivariable linear regression model[a]	
	n	FGF21 level (pg/ml)	*n*	FGF21 level (pg/ml)	Coefficient (SE)	*p* value	Coefficient (SE)	*p* value
Any anti-thrombotic	6,662	313 (205-478)	3,035	322 (205-492)	0.010 (0.016)	0.53	-0.038 (0.016)	0.02
Aspirin	6,896	315 (206-480)	2,801	317 (204-490)	0.001 (0.016)	0.96	-0.038 (0.016)	0.02
Other	9,395	314 (205-482)	302	347 (222-517)	0.051 (0.041)	0.22	-0.047 (0.040)	0.24
Angiotensin-converting enzyme inhibitor	6,453	307 (200-470)	3,244	337 (218-504)	0.090 (0.015)	<0.001	0.011 (0.015)	0.46
Angiotensin II receptor antagonist	9,181	312 (204-479)	516	366 (249-535)	0.100 (0.032)	0.002	0.009 (0.031)	0.78
β blocker	8,294	309 (201-471)	1,403	363 (238-535)	0.128 (0.020)	<0.001	0.033 (0.020)	0.10
Calcium antagonist	7,821	310 (203-474)	1,876	340 (221-512)	0.065 (0.018)	<0.001	0.017 (0.018)	0.33
Nitrate	9,153	313 (204-480)	544	351 (244-526)	0.112 (0.031)	<0.001	0.003 (0.033)	0.94
Diuretic	8,233	305 (199-463)	1,464	388 (250-597)	0.206 (0.020)	<0.001	0.082 (0.020)	<0.001

FGF21 levels are expressed as median (IQR) and $\log_e$-transformed before analysis.

[a]Adjusted for all the significant variables in the multivariable analysis in ESM Table 3.

ESM Table 6 Association of plasma FGF21 levels at baseline with the hard endpoint (CHD event, total stroke and CVD mortality combined) over 5 years using Cox regression analysis

Outcome	Number of cases (%)	HR (95% CI) Model 1[a]	Model 2[b]
Tertile 1	220 (6.8%)	1.00 (referent)	1.00 (referent)
Tertile 2	286 (8.8%)	1.31 (1.10, 1.57)	1.21 (1.00, 1.46)
Tertile 3	344 (10.6%)	1.60 (1.35, 1.90)	1.29 (1.07, 1.57)
Overall effect *p* value		<0.001	0.03
p value for treatment interaction		0.52	0.24
$\log_e$-transformed FGF21 level[c]	850 (8.8%)	1.18 (1.10, 1.25)	1.07 (1.00, 1.15)
p value		<0.001	0.09
p value for treatment interaction		0.33	0.25

[a]Adjusted for treatment allocation.

[b]Further adjusted for age, sex, known diabetes duration, prior history of CVD, smoking (never, former and current), BMI, HbA_{1c}, HOMA-IR, systolic BP, HDL cholesterol, LDL cholesterol, triacylglycerol, fibrinogen, plasma creatinine and homocysteine at baseline.

[c]HR was expressed per one SD (geometric SD = 2 pg/ml) increase in $\log_e$-transformed FGF21 levels.

ESM Table 7 Association of $\log_e$-transformed FGF21 levels at baseline with primary, secondary and tertiary outcome events over 5 years using Cox regression analysis

Outcome	Number of cases (%)	Model 1[a] HR (95% CI)	*p* value	*p* value for treatment interaction	Model 2[b] HR (95% CI)	*p* value	*p* value for treatment interaction
Primary outcome:							
Total CVD events	1281 (13.2%)	1.13 (1.07, 1.19)	<0.001	0.46	1.07 (1.01, 1.14)	0.03	0.30
Placebo	675 (13.9%)	1.15 (1.07, 1.24)	<0.001	-	1.10 (1.01, 1.20)	0.03	-
Fenofibrate	606 (12.5%)	1.11 (1.03, 1.20)	0.009	-	1.03 (0.94, 1.14)	0.47	-
Secondary outcomes:							
CHD event	537 (5.5%)	1.17 (1.08, 1.27)	<0.001	0.63	1.04 (0.94, 1.14)	0.46	0.52
Total stroke	330 (3.4%)	1.20 (1.08, 1.33)	<0.001	0.08	1.13 (1.00, 1.27)	0.05	0.04
CVD mortality	266 (2.7%)	1.28 (1.15, 1.43)	<0.001	0.56	1.10 (0.96, 1.27)	0.15	0.60
Tertiary outcomes:							
Hospitalisation for angina pectoris	455 (4.7%)	1.21 (1.11, 1.32)	<0.001	0.54	1.12 (1.01, 1.24)	0.03	0.43

HR was expressed per one SD (geometric SD = 2 pg/ml) increase in $\log_e$-transformed FGF21 levels. For the secondary outcome of coronary and carotid revascularization, analysis using $\log_e$-transformed FGF21 levels was not performed due to the non-linear relationship between $\log_e$-transformed FGF21 levels and the outcome.

[a]Adjusted for treatment allocation.

[b]Further adjusted for age, sex, known diabetes duration, prior history of CVD, smoking (never, former and current), BMI, HbA_{1c}, HOMA-IR, systolic BP, HDL cholesterol, LDL cholesterol, triacylglycerol, fibrinogen, plasma creatinine and homocysteine at baseline.

ESM Table 8 Assessing the incremental predictive value of FGF21 by comparing the C-statistics of the models with and without log$_e$-transformed FGF21 levels as well as the goodness of fit of the models using the Gronnesby and Borgan test

Model	C-statistics	*p* value	Gronnesby and Borgan test Chi-square	*p* value
Total CVD events				
All subjects				
Model 1	0.711	-	17.8	0.04
Model 1 + FGF21 (log$_e$-transformed)	0.712	0.60	15.9	0.07
Placebo				
Model 1	0.709	-	8.7	0.46
Model 1 + FGF21 (log$_e$-transformed)	0.709	0.73	8.4	0.49
Fenofibrate				
Model 1	0.707	-	6.7	0.67
Model 1 + FGF21 (log$_e$-transformed)	0.707	0.21	5.7	0.77
CHD event				
Model 1	0.736	-	9.3	0.41
Model 1 + FGF21 (log$_e$-transformed)	0.736	0.78	11.5	0.24
Total stroke				
Model 1	0.727	-	8.9	0.18
Model 1 + FGF21 (log$_e$-transformed)	0.728	0.65	8.5	0.20
CVD mortality				
Model 1	0.805	-	11.4	0.04
Model 1 + FGF21 (log$_e$-transformed)	0.805	0.86	9.4	0.09
Coronary & carotid revascularisation				
Model 1	0.708	-	10.8	0.29
Model 1 + FGF21 (log$_e$-transformed)	0.709	0.27	12.6	0.18
Hospitalisation for angina pectoris				
Model 1	0.692	-	5.3	0.81
Model 1 + FGF21 (log$_e$-transformed)	0.698	0.03	7.8	0.55

Model 1 included treatment allocation, age, sex, known diabetes duration, prior history of CVD, smoking (never, former and current), BMI, HbA$_{1c}$, HOMA-IR, systolic BP, HDL cholesterol, LDL cholesterol, triacylglycerol, fibrinogen, plasma creatinine and homocysteine at baseline.

The C-statistic measures discrimination and estimates the probability that, of two randomly chosen patients, the patient with the higher predicted risk will remain event-free longer than the patient with the lower predicted risk. A C-statistic near 0.5 indicates the predicted score is no better than a coin-flip in determining which patient will remain event-free longer. The Gronnesby and Borgan test assesses the overall fit of a model based on grouping the subjects by their estimated risk score and comparing the number of observed and model-based

estimated number of expected events within each group. A significant test result indicates differences between observed and expected numbers of events and hence lack of fit.

ESM Table 9 Association of plasma FGF21 levels at baseline with total CVD events over 5 years in different subgroups among the placebo group

Subgroup	Number of cases (%)	HR (95% CI)[a]
Age (years)		
<65 (*n*=2,875)		
Tertile 1	94 (9.5%)	1.00 (referent)
Tertile 2	127 (12.9%)	1.43 (1.07, 1.91)
Tertile 3	112 (12.3%)	1.33 (0.97, 1.82)
Overall effect *p* value		0.05
≥65 (*n*=1,968)		
Tertile 1	75 (12.2%)	1.00 (referent)
Tertile 2	132 (20.4%)	1.73 (1.28, 2.34)
Tertile 3	135 (19.1%)	1.48 (1.07, 2.04)
Overall effect *p* value		0.002
p value for interaction		0.56
Sex		
Female (*n*=1,812)		
Tertile 1	36 (7.3%)	1.00 (referent)
Tertile 2	55 (9.5%)	1.43 (0.90, 2.27)
Tertile 3	83 (11.2%)	1.38 (0.87, 2.19)
Overall effect *p* value		0.28
Male (*n*=3,031)		
Tertile 1	133 (12.0%)	1.00 (referent)
Tertile 2	204 (19.4%)	1.55 (1.23, 1.96)
Tertile 3	164 (18.8%)	1.35 (1.05, 1.75)
Overall effect *p* value		0.001
p value for interaction		0.92
Previous CVD		
Yes (*n*=1,045)		
Tertile 1	64 (23.0%)	1.00 (referent)
Tertile 2	97 (26.4%)	1.25 (0.89, 1.77)
Tertile 3	104 (26.0%)	1.09 (0.76, 1.57)
Overall effect *p* value		0.39
No (*n*=3,798)		
Tertile 1	105 (7.9%)	1.00 (referent)
Tertile 2	162 (12.8%)	1.70 (1.31, 2.21)
Tertile 3	143 (11.8%)	1.56 (1.17, 2.06)
Overall effect *p* value		<0.001
p value for interaction		0.43
BMI (kg/m^2)		
<30 (*n*=2,509)		
Tertile 1	101 (10.1%)	1.00 (referent)
Tertile 2	143 (17.4%)	1.75 (1.33, 2.30)
Tertile 3	115 (16.7%)	1.53 (1.13, 2.07)
Overall effect *p* value		<0.001
≥30 (*n*=2,329)		
Tertile 1	68 (11.3%)	1.00 (referent)
Tertile 2	116 (14.4%)	1.25 (0.91, 1.73)

Tertile 3	131 (14.2%)	1.12 (0.81, 1.56)
Overall effect *p* value		0.37
p value for interaction		0.37

Smoking
  Never (*n*=1,926)

Tertile 1	67 (9.7%)	1.00 (referent)
Tertile 2	86 (13.5%)	1.62 (1.14, 2.31)
Tertile 3	79 (13.2%)	1.52 (1.04, 2.23)
Overall effect *p* value		0.02

  Ever (*n*=2,917)

Tertile 1	102 (11.2%)	1.00 (referent)
Tertile 2	173 (17.5%)	1.52 (1.17, 1.97)
Tertile 3	168 (16.6%)	1.35 (1.03, 1.78)
Overall effect *p* value		0.007
p value for interaction		0.98

Known diabetes duration (years)
  <5 (median) (*n*=2,289)

Tertile 1	53 (7.2%)	1.00 (referent)
Tertile 2	95 (12.0%)	1.66 (1.16, 2.38)
Tertile 3	100 (13.2%)	1.68 (1.15, 2.45)
Overall effect *p* value		0.01

  ≥5(median) (*n*=2,546)

Tertile 1	115 (13.4%)	1.00 (referent)
Tertile 2	164 (19.7%)	1.46 (1.13, 1.90)
Tertile 3	147 (17.2%)	1.13 (0.86, 1.50)
Overall effect *p* value		0.009
p value for interaction		0.14

HbA_{1c}
  <7.0% (53.0 mmol/mol) (*n*=2,636)

Tertile 1	73 (8.4%)	1.00 (referent)
Tertile 2	126 (13.7%)	1.46 (1.08, 1.99)
Tertile 3	98 (11.6%)	1.20 (0.86, 1.69)
Overall effect *p* value		0.04

  ≥7.0% (53.0 mmol/mol) (*n*=2,207)

Tertile 1	96 (13.2%)	1.00 (referent)
Tertile 2	133 (18.7%)	1.55 (1.16, 2.06)
Tertile 3	149 (19.4%)	1.47 (1.09, 1.98)
Overall effect *p* value		0.009
p value for interaction		0.95

Total cholesterol (mmol/l)
  <4.5 (*n*=1,113)

Tertile 1	34 (8.7%)	1.00 (referent)
Tertile 2	45 (13.3%)	1.42 (0.88, 2.30)
Tertile 3	61 (15.9%)	1.70 (1.05, 2.75)
Overall effect *p* value		0.10

  4.5-5.5 (*n*=2,459)

Tertile 1	106 (12.7%)	1.00 (referent)
Tertile 2	147 (17.2%)	1.51 (1.15, 1.98)

Tertile 3	103 (13.4%)	1.03 (0.76, 1.41)
Overall effect *p* value		0.002
>5.5 (*n*=1,271)		
Tertile 1	29 (7.8%)	1.00 (referent)
Tertile 2	67 (15.3%)	1.94 (1.22, 3.10)
Tertile 3	83 (18.1%)	2.01 (1.25, 3.23)
Overall effect *p* value		0.009
p value for interaction		0.009
HDL cholesterol		
Low (*n*=2,858)[b]		
Tertile 1	93 (11.5%)	1.00 (referent)
Tertile 2	166 (17.0%)	1.57 (1.19, 2.06)
Tertile 3	172 (16.1%)	1.39 (1.04, 1.85)
Overall effect *p* value		0.006
High (*n*=1,985)		
Tertile 1	76 (9.6%)	1.00 (referent)
Tertile 2	93 (14.3%)	1.48 (1.07, 2.05)
Tertile 3	75 (13.8%)	1.34 (0.94, 1.92)
Overall effect *p* value		0.06
p value for interaction		0.94
LDL cholesterol (mmol/l)		
<3.0 (*n*=2,193)		
Tertile 1	68 (10.1%)	1.00 (referent)
Tertile 2	109 (15.5%)	1.47 (1.06, 2.04)
Tertile 3	108 (13.2%)	1.15 (0.81, 1.62)
Overall effect *p* value		0.04
3.0-3.5 (*n*=1,406)		
Tertile 1	59 (11.9%)	1.00 (referent)
Tertile 2	85 (16.8%)	1.55 (1.08, 2.23)
Tertile 3	68 (16.8%)	1.28 (0.85, 1.93)
Overall effect *p* value		0.06
>3.5 (*n*=1,244)		
Tertile 1	42 (9.7%)	1.00 (referent)
Tertile 2	65 (15.5%)	1.66 (1.10, 2.52)
Tertile 3	71 (18.3%)	1.84 (1.19, 2.83)
Overall effect *p* value		0.02
p value for interaction		0.37
Triacylglycerol (mmol/l)		
≥1.7 (*n*=2,498)		
Tertile 1	55 (10.1%)	1.00 (referent)
Tertile 2	155 (17.5%)	1.69 (1.23, 2.33)
Tertile 3	173 (16.2%)	1.45 (1.05, 2.01)
Overall effect *p* value		0.005
<1.7 (*n*=2,345)		
Tertile 1	114 (10.8%)	1.00 (referent)
Tertile 2	104 (14.0%)	1.40 (1.05, 1.86)
Tertile 3	74 (13.5%)	1.31 (0.94, 1.83)
Overall effect *p* value		0.06
p value for interaction		0.56

Estimated GFR (ml min^{-1} 1.73 m^{-2})		
<90 (*n*=2,850)		
Tertile 1	97 (10.9%)	1.00 (referent)
Tertile 2	167 (17.9%)	1.74 (1.33, 2.28)
Tertile 3	180 (17.5%)	1.62 (1.22, 2.14)
Overall effect *p* value		<0.001
≥90 (*n*=1,993)		
Tertile 1	72 (10.1%)	1.00 (referent)
Tertile 2	92 (13.2%)	1.27 (0.90, 1.77)
Tertile 3	67 (11.5%)	1.09 (0.75, 1.59)
Overall effect *p* value		0.36
p value for interaction		0.35

As the relationship between $\log_e$-transformed FGF21 levels and total CVD events among the placebo group showed significant deviation from linearity (*p*=0.02), analysis was not performed using $\log_e$-transformed FGF21 levels.

[a]Adjusted for (except in its subgroup analysis): age, sex, known diabetes duration, prior history of CVD, smoking (never, former and current), BMI, HbA$_{1c}$, HOMA-IR, systolic BP, HDL cholesterol, LDL cholesterol, triacylglycerol, fibrinogen, plasma creatinine (except in subgroup analysis by estimated GFR) and homocysteine at baseline.

[b]<1.03 mmol/l for men and <1.29 mmol/l for women.