

Supplemental Material

Additional file: Table S1. Baseline characteristics of the study population by screening renal function strata

Characteristics	eGFR \geq 60 stratum	eGFR<60 stratum	p-value
N.	3946	1434	
Age (yrs), mean \pm SD	59.0 \pm 9.4	66.0 \pm 9.5	<0.001
Age \geq 65 yrs	1103 (28.0%)	804 (56.1%)	<0.001
Male sex	2840 (72.0%)	811 (56.6%)	<0.001
Diabetes duration (yrs), median (IQR)	6.3 (2.3, 11.8)	10.3 (4.4, 17.0)	<0.001
BMI (kg/m ²), mean \pm SD	29.6 \pm 5.5	29.3 \pm 5.8	0.080
Race			<0.001
White	2935 (74.4%)	974 (67.9%)	
Asian	729 (18.5%)	360 (25.1%)	
Black	162 (4.1%)	54 (3.8%)	
Other	120 (3.0%)	46 (3.2%)	
Geographic Region			<0.001
United States, Canada	626 (15.9%)	227 (15.8%)	
Mexico, Central/South America	1014 (25.7%)	379 (26.4%)	
Western Europe, Australia, New Zealand, Middle East	474 (12.0%)	142 (9.9%)	
Eastern Europe, Africa	1162 (29.4%)	346 (24.1%)	
Asia/Pacific	670 (17.0%)	340 (23.7%)	
Smoking	627 (15.9%)	107 (7.5%)	<0.001
Hypertension	3176 (80.5%)	1293 (90.2%)	<0.001
Previous MI	3459 (87.7%)	1275 (88.9%)	0.21
PCI	2501 (63.4%)	871 (60.7%)	0.077
CABG	458 (11.6%)	230 (16.0%)	<0.001
HF history	975 (24.7%)	558 (38.9%)	<0.001
Previous stroke	234 (5.9%)	154 (10.7%)	<0.001
PAD	309 (7.8%)	205 (14.3%)	<0.001
AFib	209 (5.3%)	167 (11.6%)	<0.001
eGFR* (ml/min/1.73m ²), mean \pm SD	79.5 \pm 16.8	47.4 \pm 13.7	<0.001
Index ACS Event Type			0.36
Myocardial Infarction	3034 (77.1%)	1118 (78.2%)	
Unstable Angina	903 (22.9%)	311 (21.8%)	
Time from index ACS to randomization, median (IQR)	44.0 (30.0, 63.0)	43.0 (30.0, 65.0)	0.90
Troponin I (ng/L), median (IQR)	7.7 (4.0, 16.9)	13.3 (6.7, 29.2)	<0.001
Heart rate (bpm), mean \pm SD	71.5 \pm 10.6	70.8 \pm 11.2	0.031
SBP (mmHg), mean \pm SD	128.2 \pm 16.3	131.1 \pm 17.4	<0.001
DBP (mmHg), mean \pm SD	76.8 \pm 9.4	75.4 \pm 10.2	<0.001
Total cholesterol (mg/dL), mean \pm SD	152.6 \pm 42.7	159.2 \pm 46.5	<0.001
LDL cholesterol (mg/dL), mean \pm SD	43.0 \pm 10.4	43.4 \pm 11.2	0.23
HDL cholesterol (mg/dL), mean \pm SD	77.3 \pm 33.4	82.2 \pm 37.9	<0.001
Triglycerides (mg/dL), mean \pm SD	163.2 \pm 107.1	168.2 \pm 94.5	0.12
UACR (mg/g creat.), median (IQR)	3.4 (1.6, 10.0)	9.7 (2.9-50.6)	<0.001
C-reactive protein (mg/dL), mean \pm SD	5.1 \pm 12.3	6.9 \pm 17.0	<0.001
Antiplatelet agents	3844 (97.4%)	1388 (96.8%)	0.22

Beta-blockers	3247 (82.3%)	1164 (81.2%)	0.35
ACEi/ARBs	3267 (82.8%)	1144 (79.8%)	0.011
Statins	3594 (91.1%)	1272 (88.7%)	0.009
Antidiabetic agents	3916 (99.2%)	1409 (98.3%)	0.002
Insulin	1076 (27.3%)	529 (36.9%)	<0.001
Metformin	2861 (72.5%)	701 (48.9%)	<0.001
Thiazolidinediones	83 (2.1%)	48 (3.3%)	0.009
Sulfonylureas	1873 (47.5%)	630 (43.9%)	0.022
Calcium channel blockers	763 (19.3%)	434 (30.3%)	<0.001
Diuretics (any)	1240 (31.4%)	774 (54.0%)	<0.001

Legend: MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary-artery bypass grafting; HF, heart failure; PAD, peripheral artery disease; AFib, atrial fibrillation; eGFR, estimated glomerular filtration rate; ACS, acute coronary syndrome; SBP, systolic blood pressure; DBP diastolic blood pressure; ACEi/ARBs, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; UACR, urinary albumin-to-creatinine ratio.

*eGFR at randomization, that occurred 9 (7-13) days after the baseline visit.

Stratification according to renal function was performed at the baseline visit, as follows: 1) "normal renal function" stratum if eGFR ≥ 60 ml/min/1.73m² or 2) "impaired renal function" stratum if eGFR < 60 ml/min/1.73m².

Additional file: Table S2. Baseline and changes from baseline to the last visit for lipoproteins, UACR and estimated glomerular filtration rate

Variable change	Placebo	Alogliptin	P-value*	Inter. P
<i>eGFR ≥60 stratum</i>				
Total cholesterol (mg/dL)				
Baseline	153±42	152±43	0.19	
Last visit: change from baseline	14±44	14±44	0.62	0.56
HDL cholesterol (mg/dL)				
Baseline	43±10	43±11	0.25	
Last visit: change from baseline	1.7±8.4	1.5±8.6	0.34	0.23
LDL cholesterol (mg/dL)				
Baseline	78±34	77±33	0.17	
Last visit: change from baseline	9.3±34.4	9.0±33.6	0.78	0.27
Triglycerides (mg/dL)				
Baseline	165±108	161±105	0.18	
Last visit: change from baseline	21±171	17±142	0.48	0.49
eGFR change from baseline	0.3±15	-0.4±14	0.11	0.15
U albumin/creatinine ratio (mg/g of creatinine)				
Baseline	17.5±54.1	18.1±69.1	0.83	
12 months: change from baseline	1.7±7.1	1.0±4.1	0.042	0.96
<i>eGFR <60 stratum</i>				
Total cholesterol (mg/dL)				
Baseline	158±46	160±47	0.62	
Last visit: change from baseline	10±47	9±41	0.55	0.56
HDL cholesterol (mg/dL)				
Baseline	44±11	43±11	0.25	
Last visit: change from baseline	1.7±9.7	1.7±9.7	0.94	0.23
LDL cholesterol (mg/dL)				
Baseline	81±37	83±39	0.24	
Last visit: change from baseline	6.8±38.8	4.7±33.4	0.29	0.27
Triglycerides (mg/dL)				
Baseline	168±98	167±91	0.84	
Last visit: change from baseline	7±93	11±99	0.39	0.49
eGFR change from baseline	0.1±11	-0.9±11	0.11	0.15
U albumin/creatinine ratio (mg/mmol of creatinine)				
Baseline	67.8±152	74.1±167	0.53	
12 months: change from baseline	2.4±17.3	5.1±46.4	0.33	0.96

Legend: HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate in ml/min/1.73m²; Inter. P, p-value for interaction between eGFR strata and treatment allocation for each outcome in a linear regression model.

*non-parametric comparisons provide similar results.

Additional file: Table S3. Major study end-points: event rates (per 100py) and event rate comparison

End-point	Placebo	Alogliptin	ARD (95%CI)	P-value*
<i>eGFR ≥60 stratum</i>				
Primary end-point	6.5 (5.6-7.4)	5.2 (4.4-6.1)	-1.3 (-2.4 to -0.4)	0.042
Components of the primary end-point				
Cardiovascular death	1.9 (1.5-2.5)	1.2 (0.8-1.62)	-0.7 (-1.4 to -0.1)	0.018
Non-fatal MI	3.8 (3.1-4.5)	3.3 (2.7-4.0)	-0.5 (-1.4 to +0.4)	0.27
Non-fatal stroke	0.6 (0.4-1.0)	0.7 (0.4-1.0)	+0.1 (-0.3 to +0.5)	0.78
Secondary end-point	7.7 (6.8-8.8)	6.3 (5.5-7.3)	-1.4 (-2.8 to -0.1)	0.042
All-cause death	2.9 (2.3-3.5)	2.3 (1.9-2.9)	-0.5 (-1.3 to +0.3)	0.22
All cardiovascular deaths	2.3 (1.8-2.9)	1.4 (1.0-1.9)	-0.9 (-1.6 to -0.2)	0.008
Heart failure hospitalization	1.4 (1.0-1.9)	1.4 (1.1-1.9)	-0.01 (-0.5 to +0.6)	0.95
<i>eGFR <60 stratum</i>				
Primary end-point	12.1 (10.2-14.5)	14.6 (12.5-17.2)	+2.5 (-0.7 to +5.7)	0.13
Components of the primary end-point				
Cardiovascular death	4.7 (3.5-6.1)	4.7 (3.6-6.2)	+0.1 (-1.8 to +1.9)	0.95
Non-fatal MI	5.8 (4.5-7.5)	8.6 (7.0-10.6)	+2.8 (+0.5 to +5.1)	0.017
Non-fatal stroke	1.2 (0.7-2.1)	0.7 (0.4-1.5)	-0.5 (-1.3 to +0.4)	0.28
Secondary end-point	13.2 (11.1-15.6)	15.5 (13.2-18.1)	+2.3 (-0.9 to + 5.6)	0.17
All-cause death	7.7 (6.2-9.5)	7.2 (5.7-8.9)	-0.5 (-2.7 to +1.8)	0.66
All cardiovascular deaths	5.3 (4.1-6.8)	6.2 (4.9-7.8)	+0.9 (-1.1 to +2.3)	0.40
Heart failure hospitalization	4.4 (3.3-5.8)	5.9 (4.6-7.6)	+1.6 (-0.3 to +3.5)	0.12

*P-values for interaction, as follows:

- Primary outcome: treatment allocation (alogliptin or placebo) * eGFR stratum, interaction P =0.018
- Cardiovascular death: treatment allocation (alogliptin or placebo) * eGFR stratum, interaction P =0.076
- Non-fatal MI: treatment allocation (alogliptin or placebo) * eGFR stratum, interaction P =0.016
- Non-fatal stroke: treatment allocation (alogliptin or placebo) * eGFR stratum, interaction P =0.29
- Secondary end-point: treatment allocation (alogliptin or placebo) * eGFR stratum, interaction P =0.028
- All-cause death: treatment allocation (alogliptin or placebo) * eGFR stratum, interaction P =0.57
- All cardiovascular deaths: treatment allocation (alogliptin or placebo) * eGFR stratum, interaction P =0.012
- Heart failure hospitalization: treatment allocation (alogliptin or placebo) * eGFR stratum, interaction P =0.33

The primary end-point was a composite of cardiovascular death, non-fatal MI and non-fatal stroke

The secondary end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal

stroke, or urgent revascularization due to unstable angina within 24 hours after hospital admission.

Legend: MI, myocardial infarction; ARD, absolute risk difference.

Additional file: Table S4. eGFR changes between the baseline and randomization visit

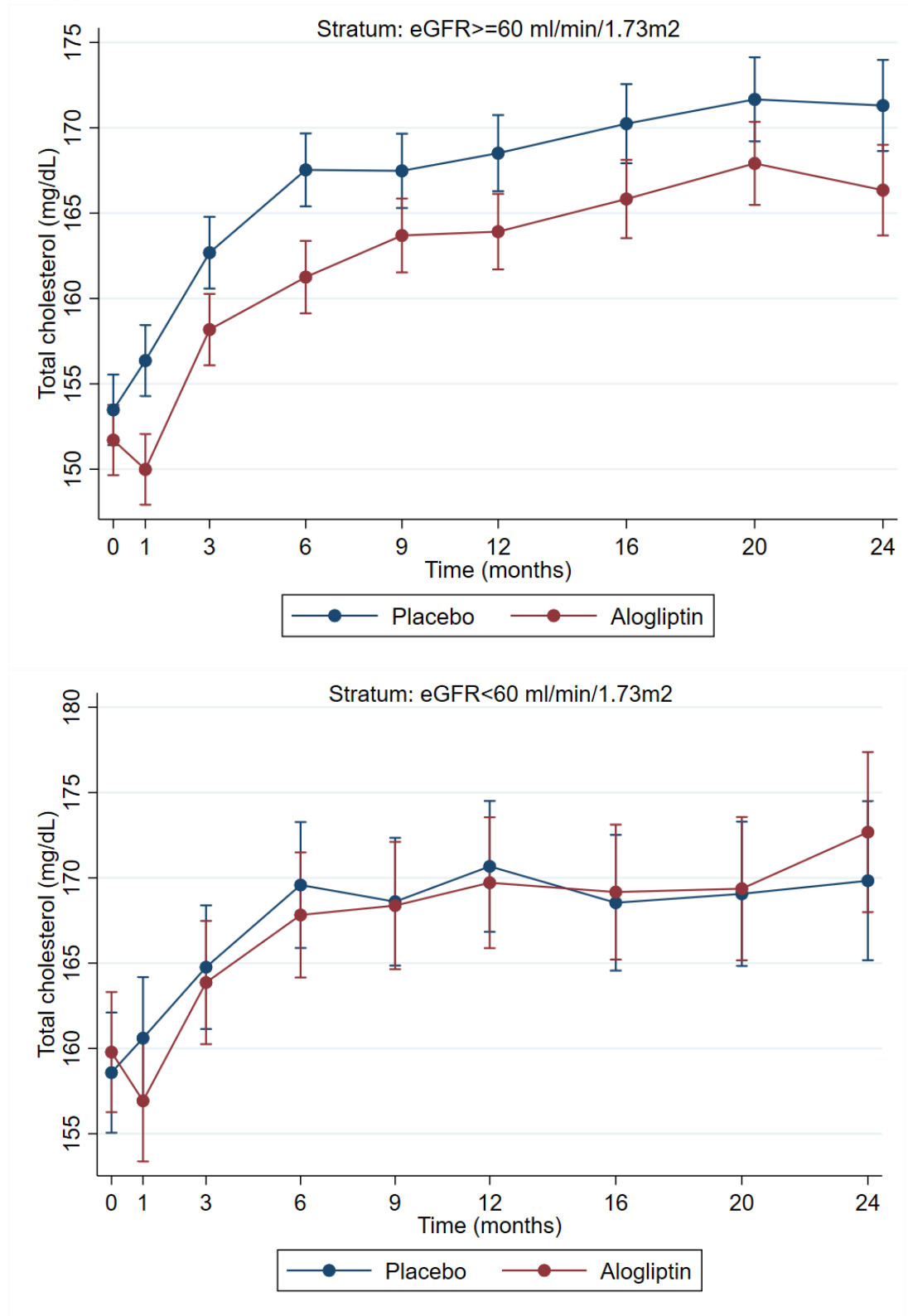
Placebo group		
eGFR categories	Baseline: eGFR \geq 60	Baseline: eGFR <60
Randomization: eGFR \geq 60	1769 (90.1%)	117 (16.3%)
Randomization: eGFR <60	194 (9.9%)	599 (83.4%)
Alogliptin group		
eGFR categories	Baseline: eGFR \geq 60	Baseline: eGFR <60
Randomization: eGFR \geq 60	1812 (91.4%)	117 (16.3%)
Randomization: eGFR <60	171 (8.6%)	601 (83.7%)

eGFR, estimated glomerular filtration rate in ml/min/1.73m²

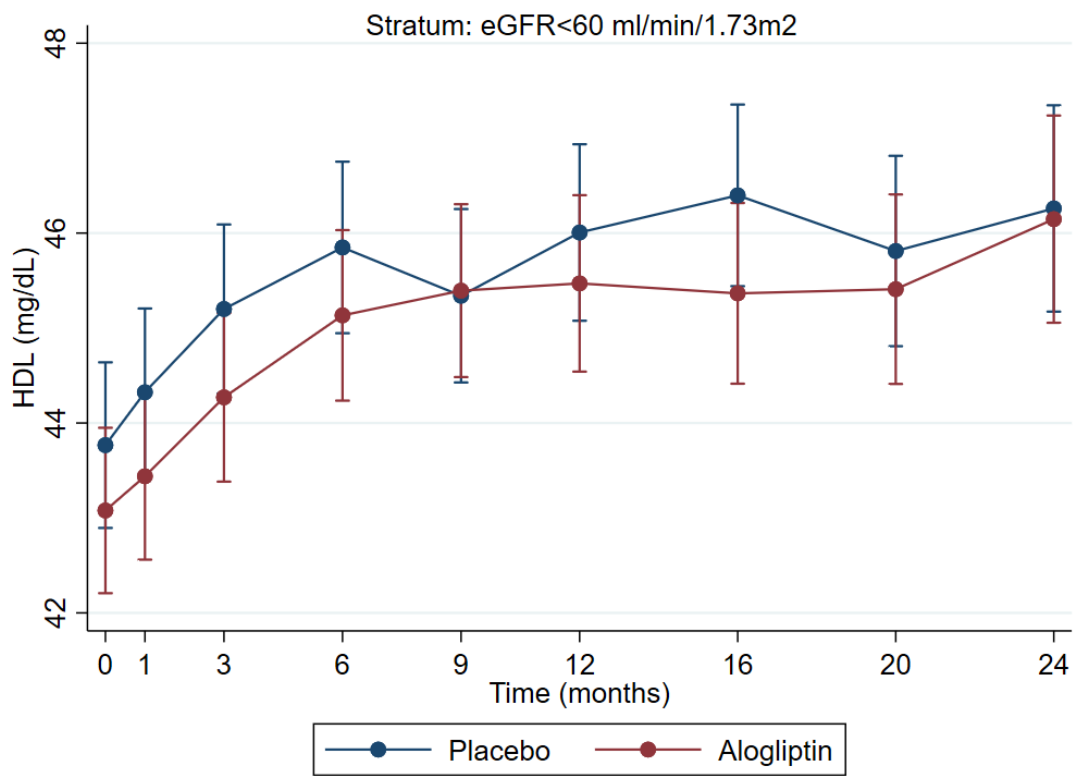
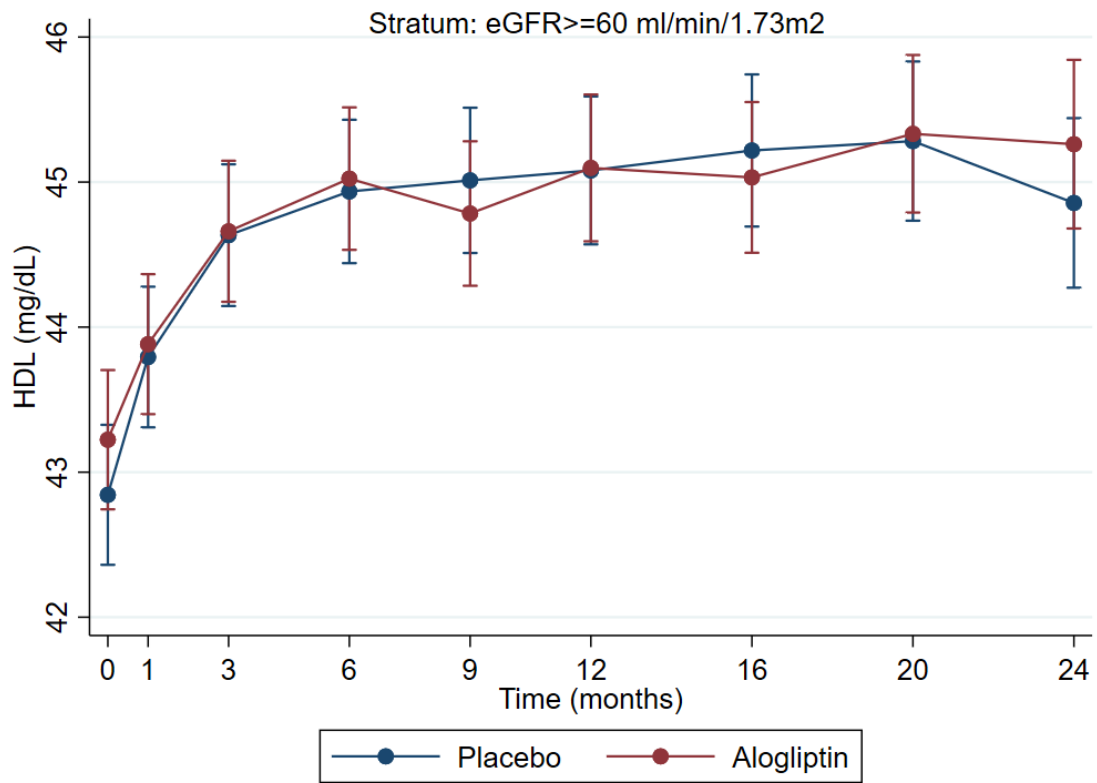
eGFR at randomization occurred 9 (7-13) days after the baseline visit where the stratification was performed.

Additional file: Figure S1. Changes from baseline by treatment arm (within each eGFR stratum) for total, LDL and HDL cholesterol, body mass index, creatinine, eGFR, UACR, systolic and diastolic blood pressure, and c-reactive protein.

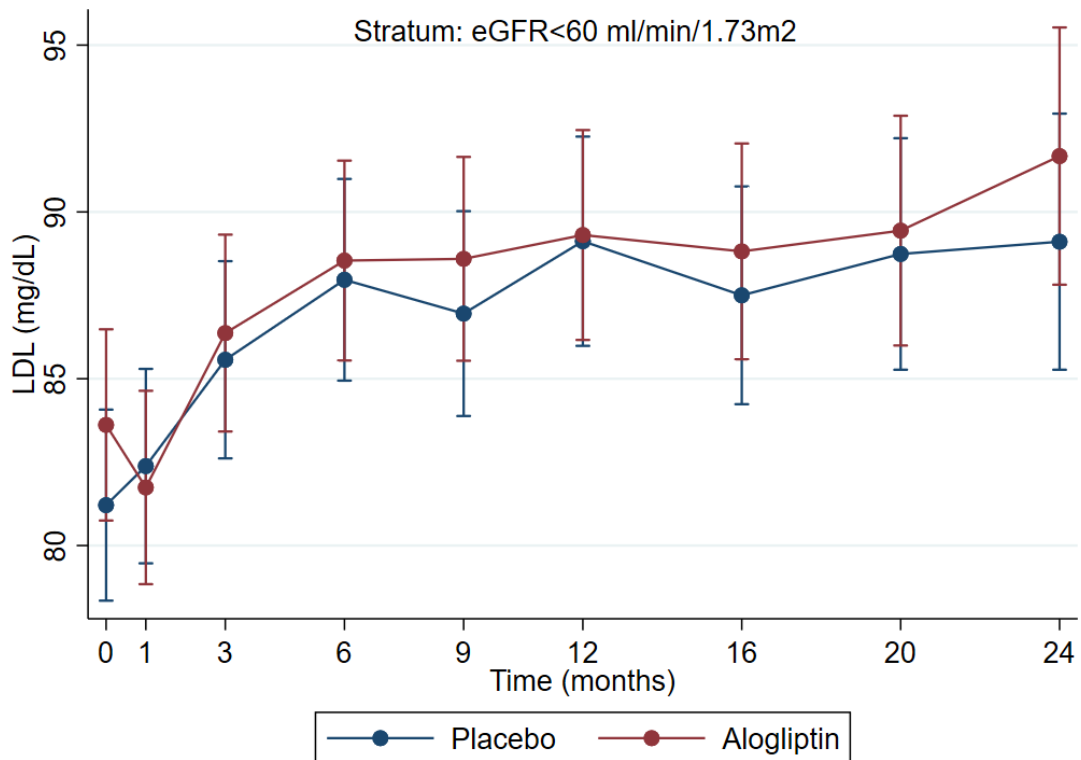
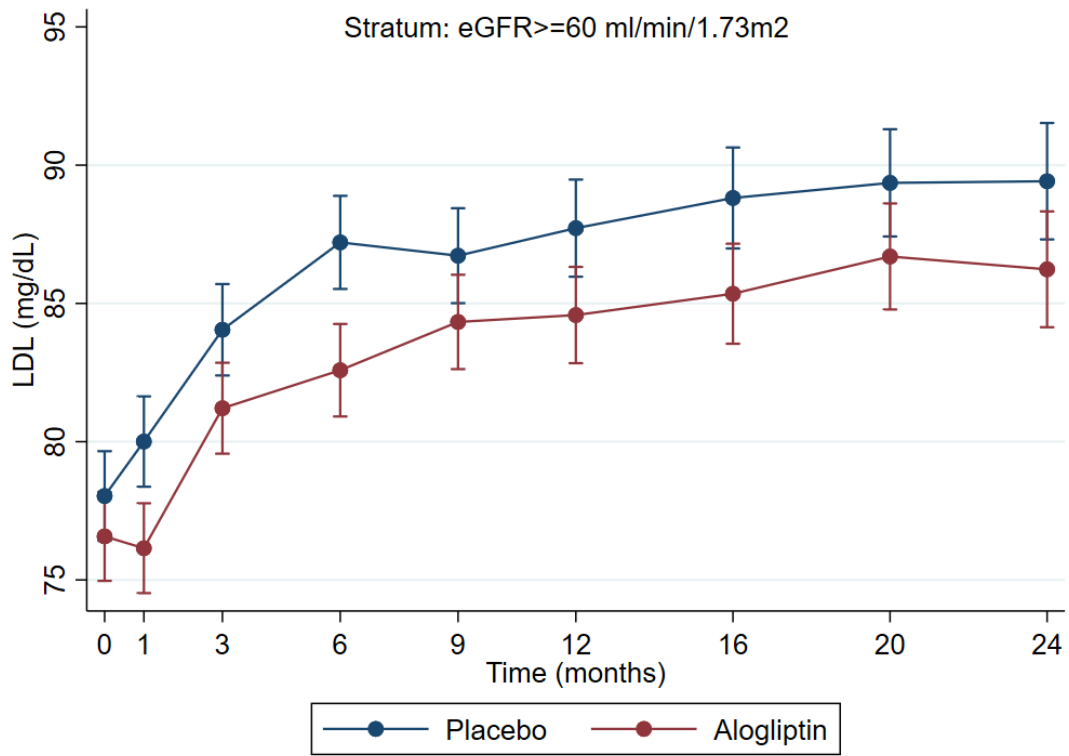
(A) Total cholesterol



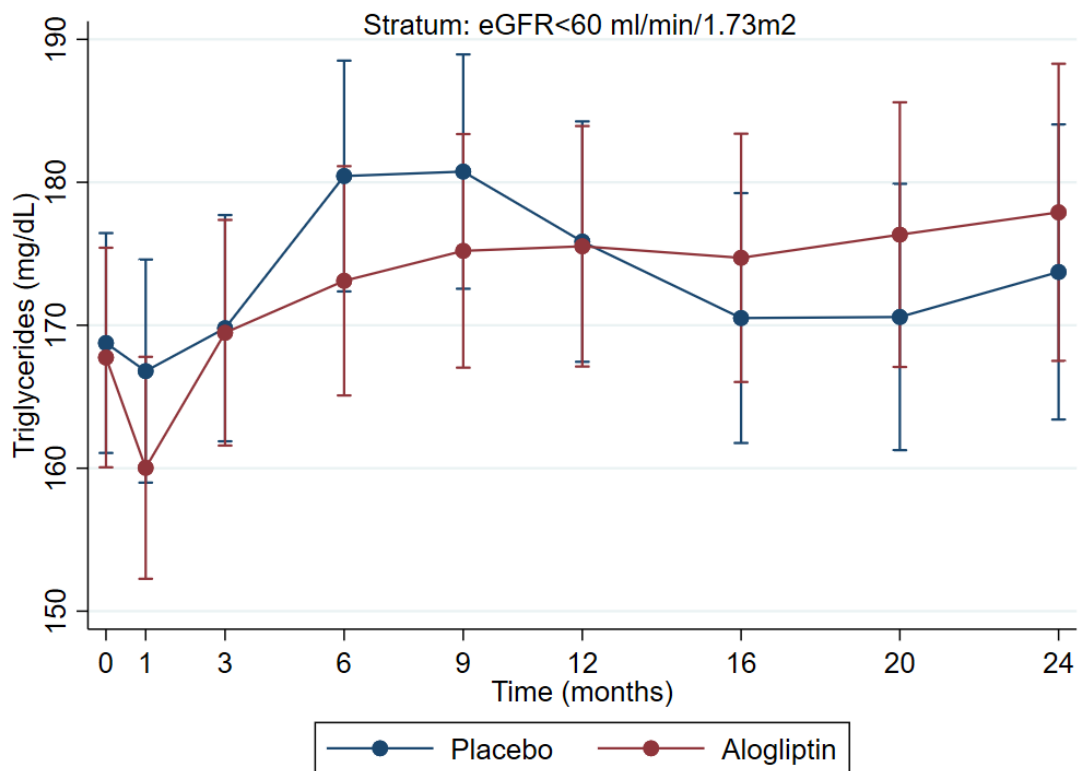
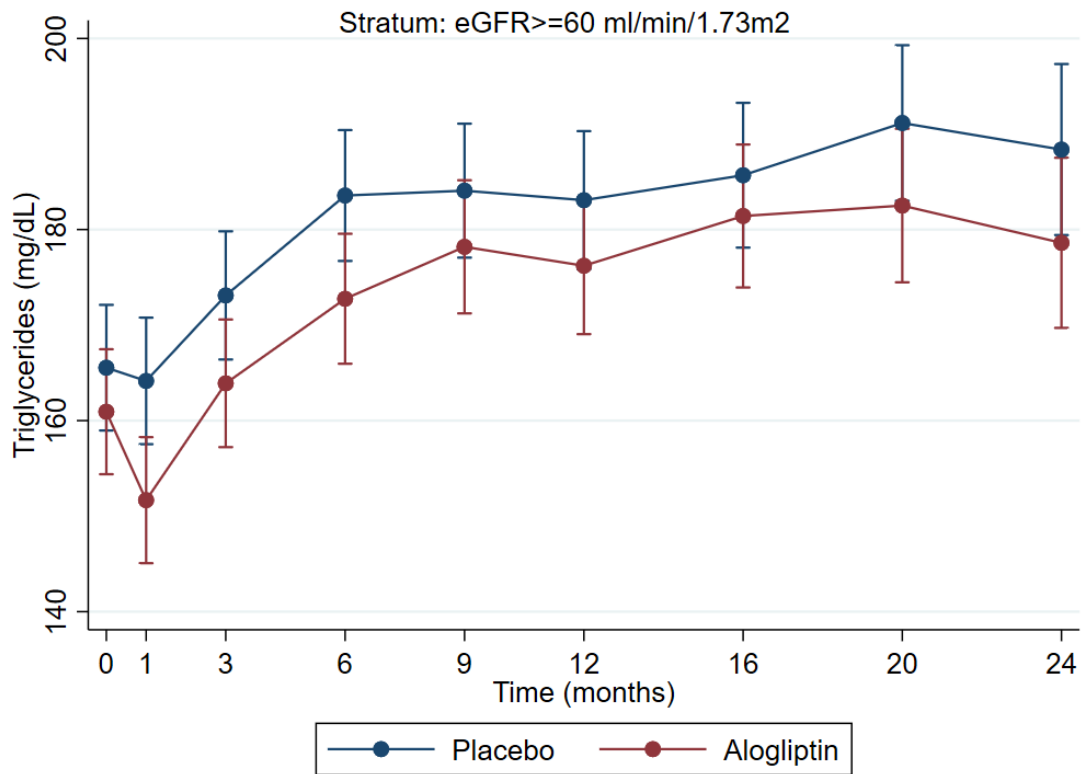
(B) HDL cholesterol



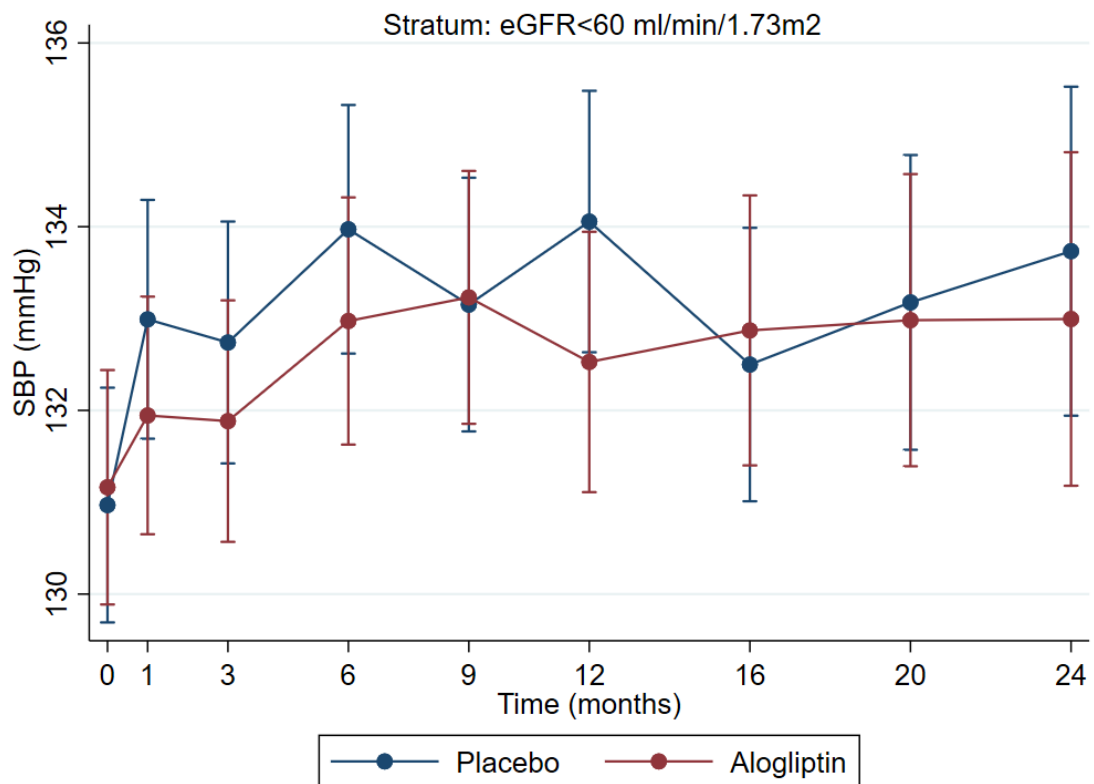
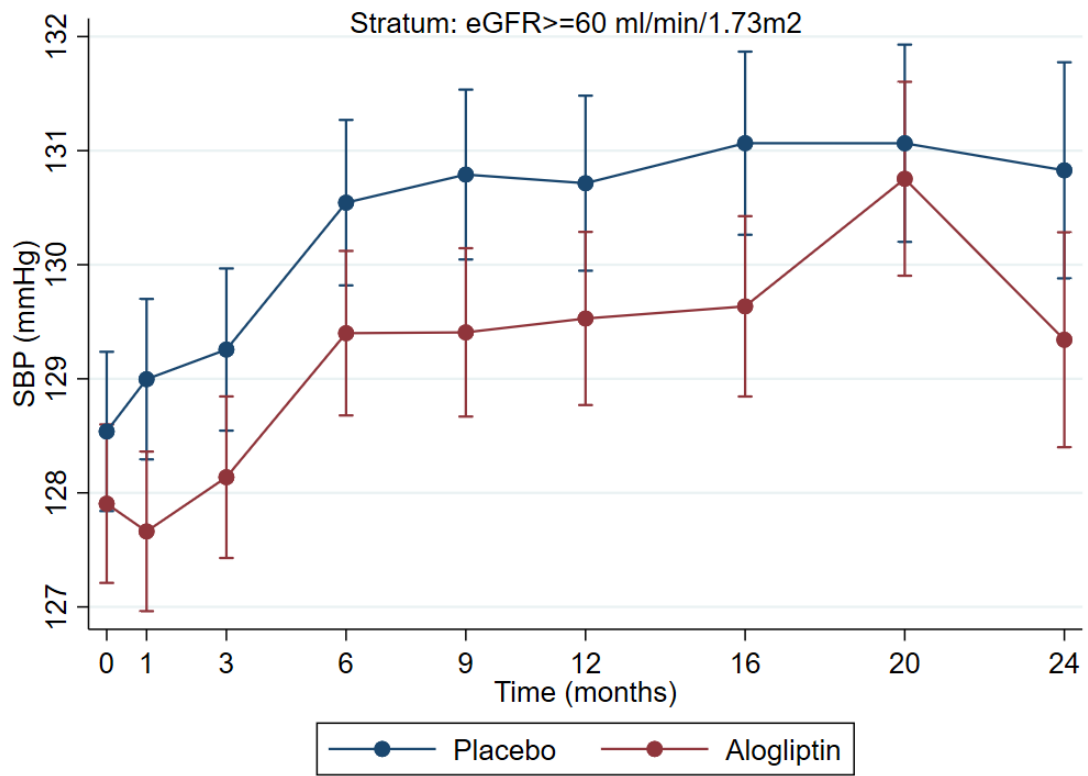
(C) LDL cholesterol



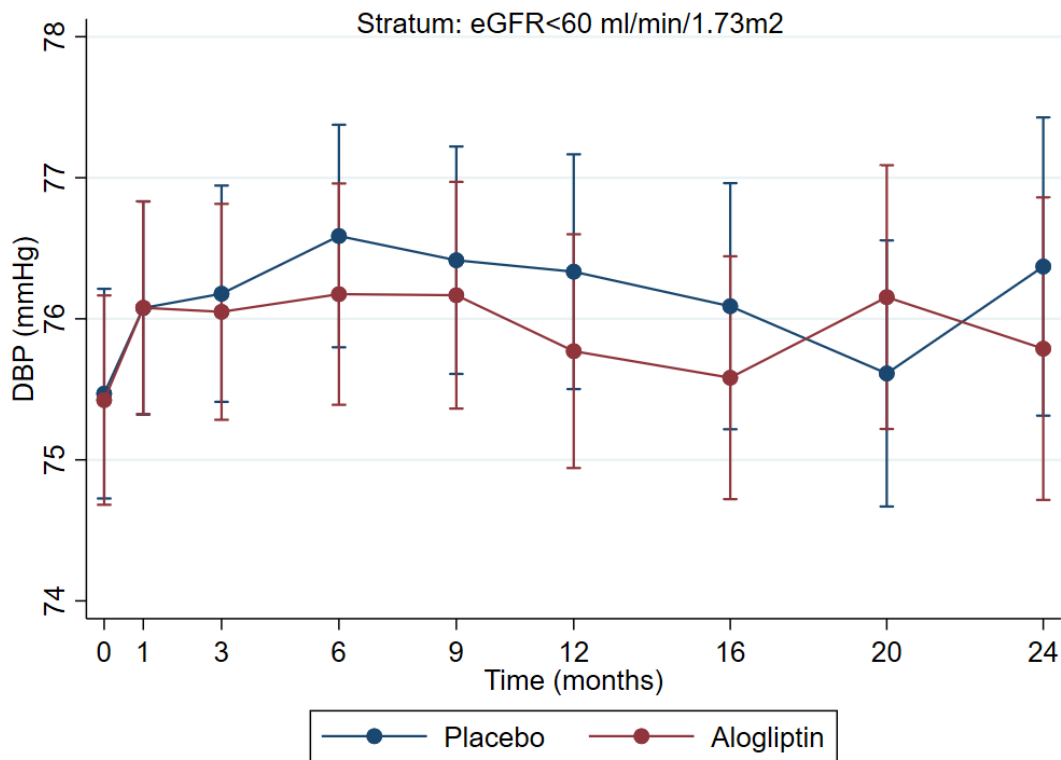
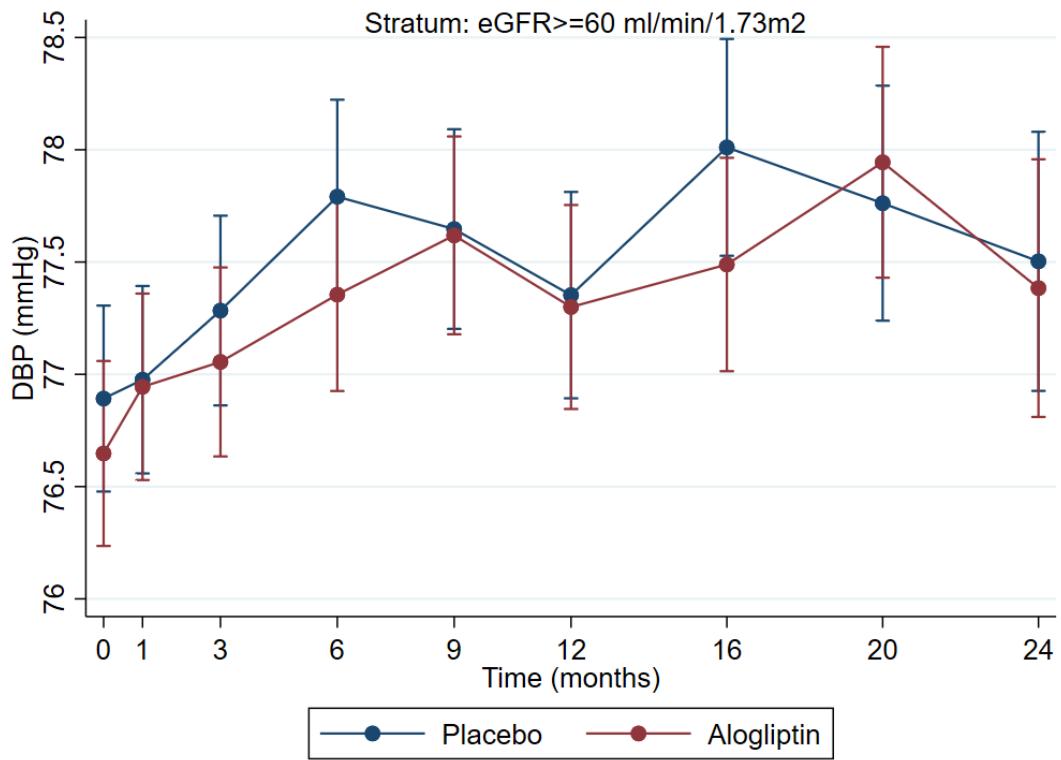
(D) Triglycerides



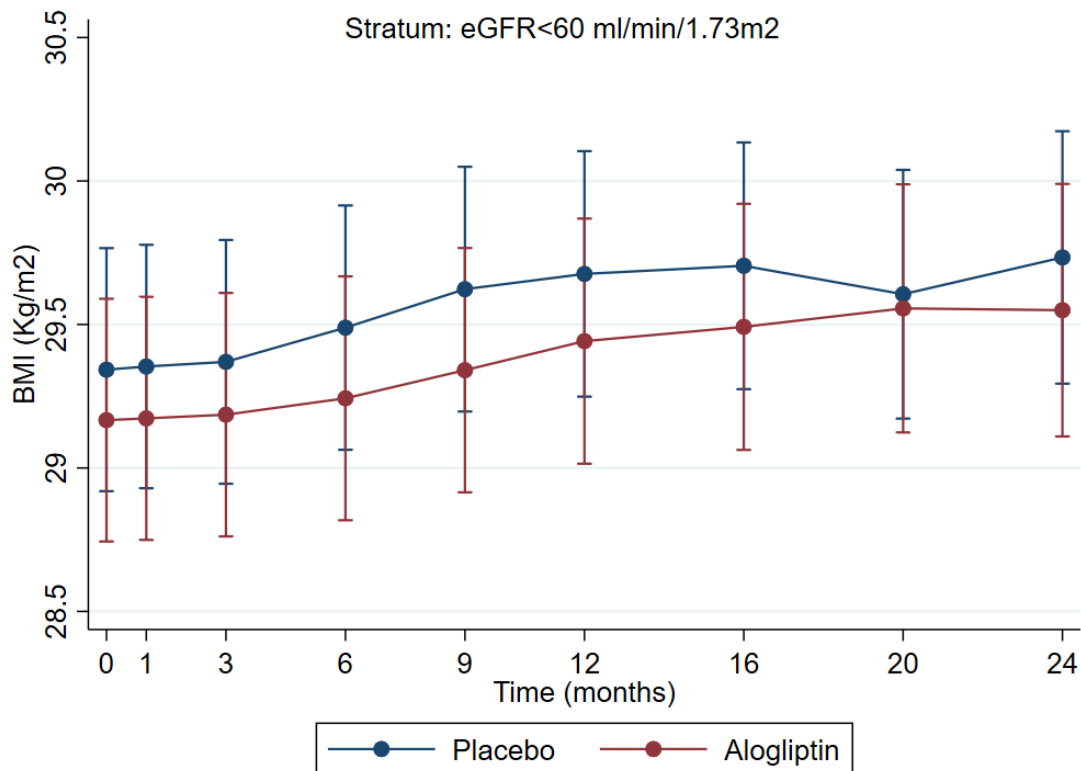
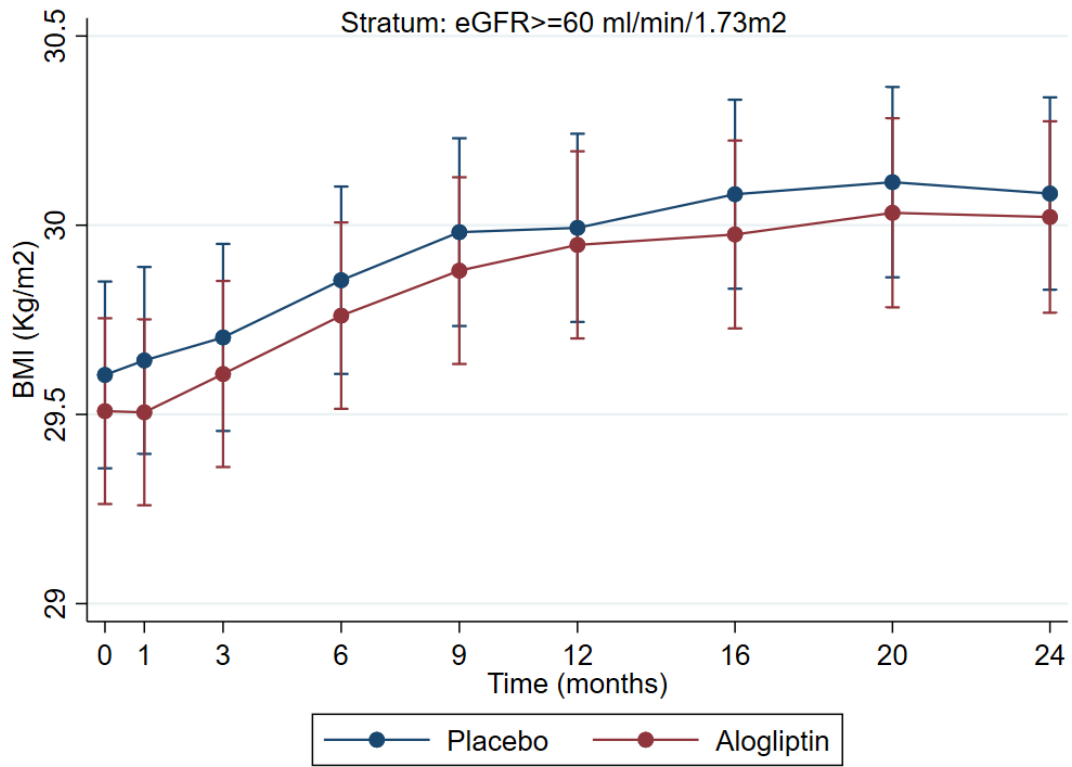
(E) SBP



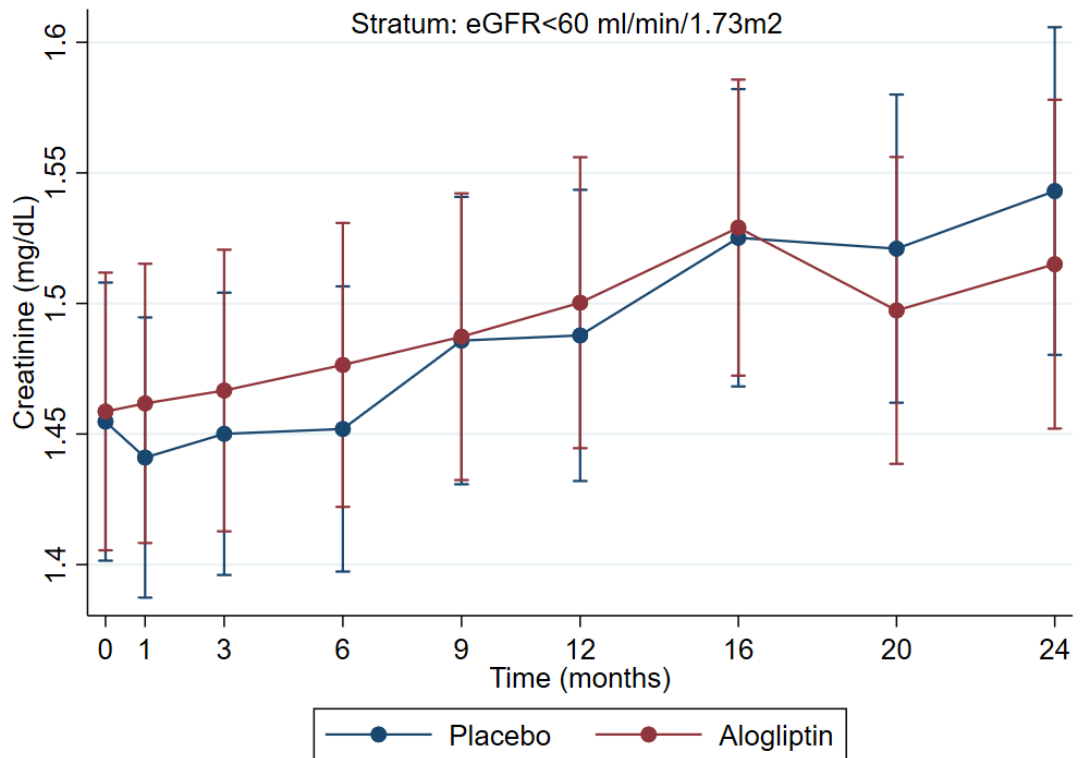
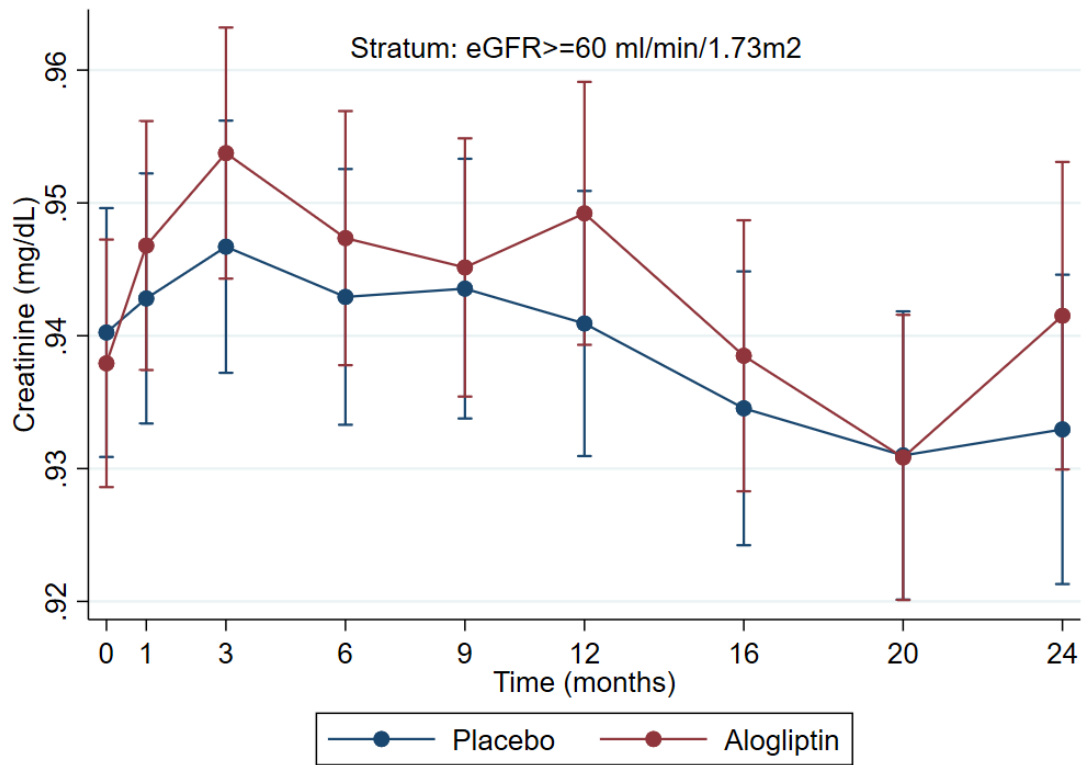
(F) DBP



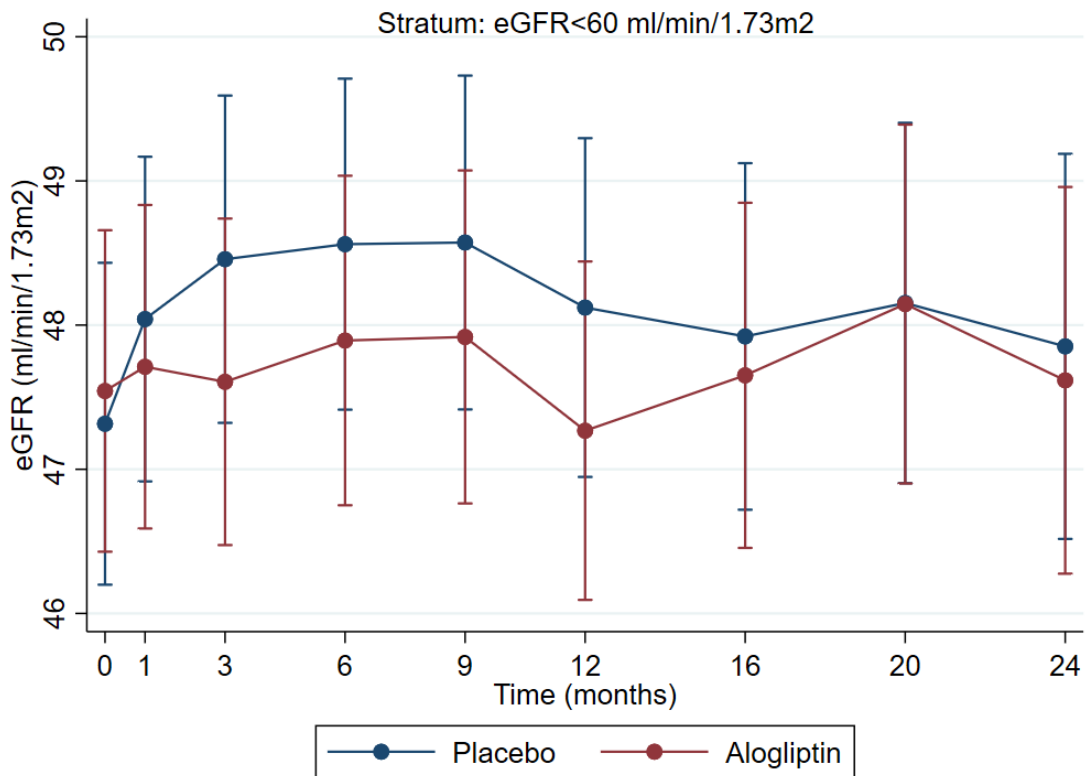
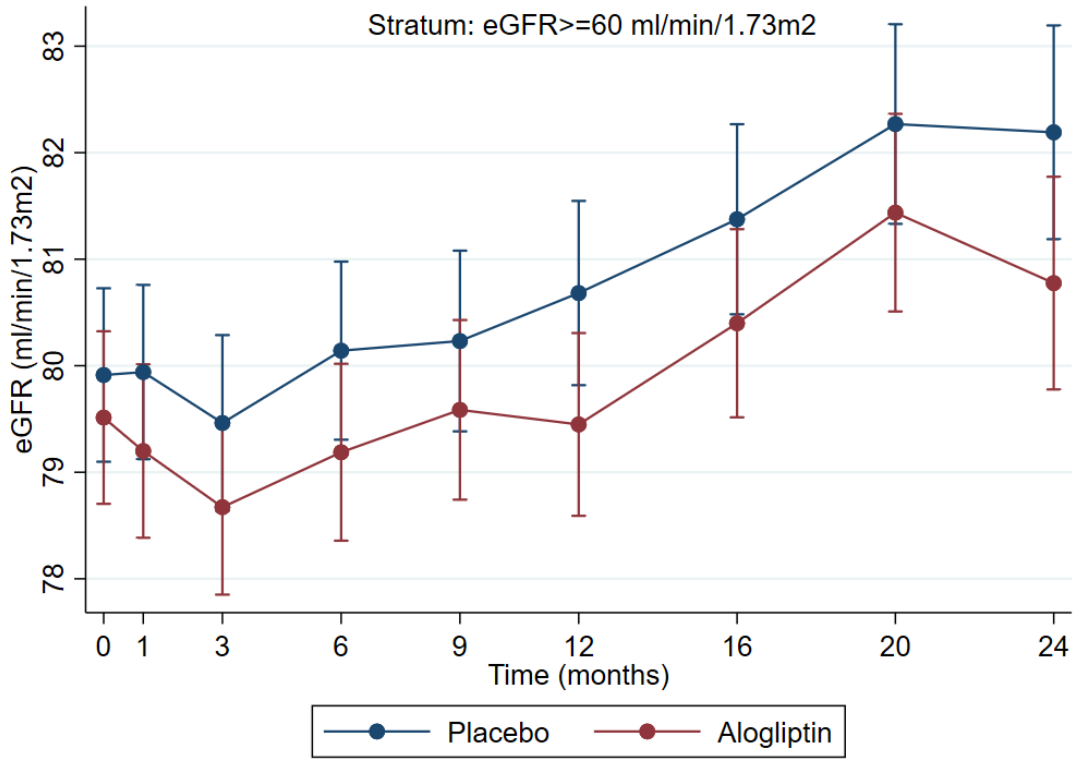
(G) BMI



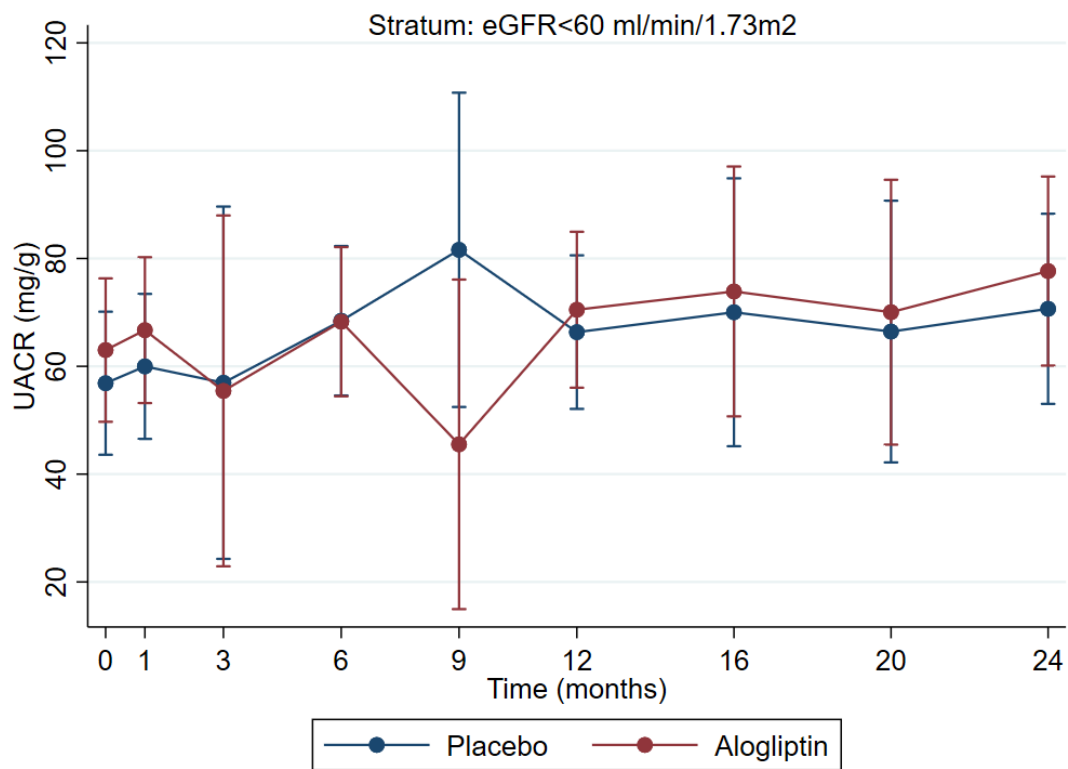
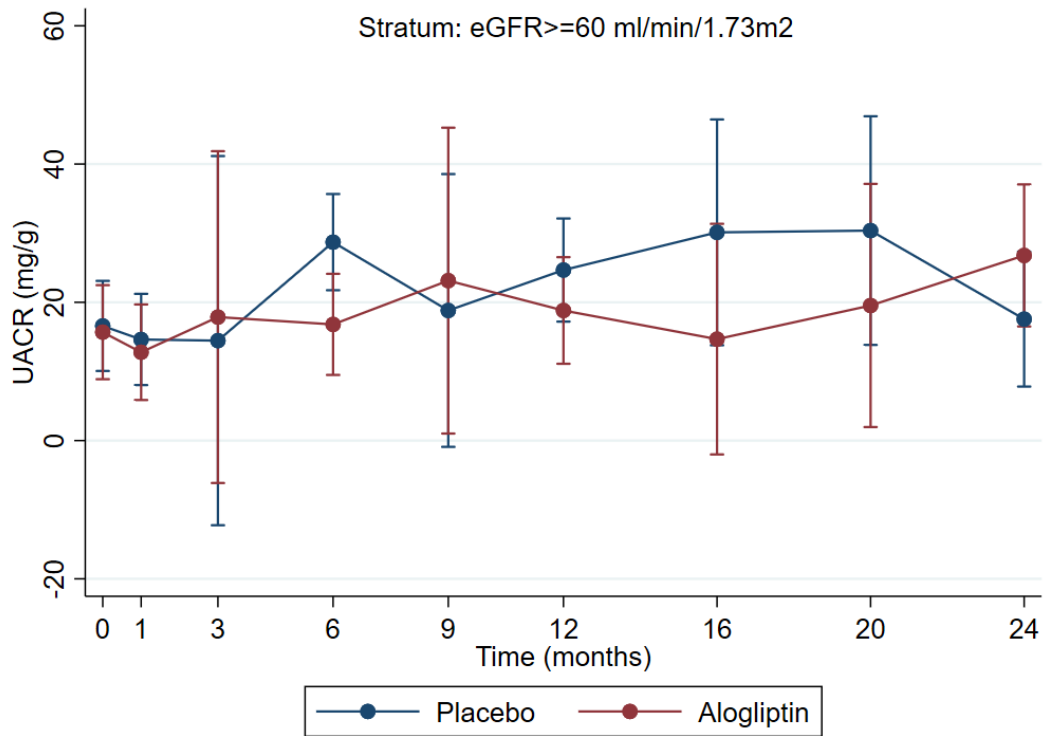
(H) Creatinine



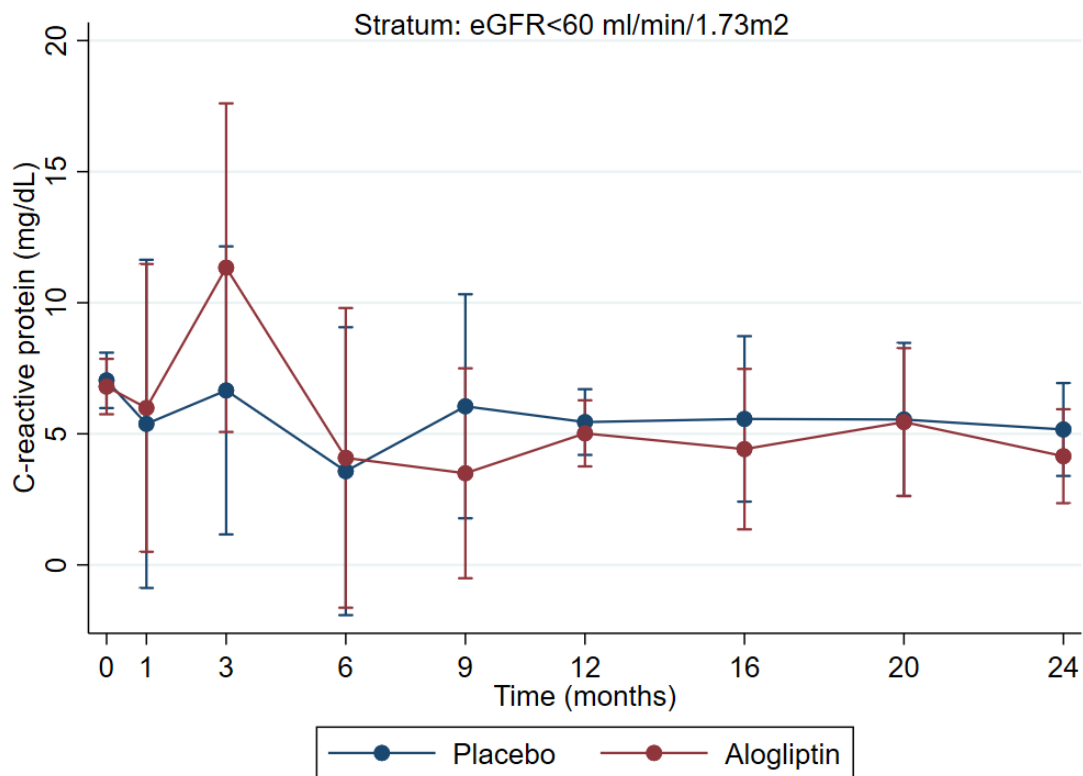
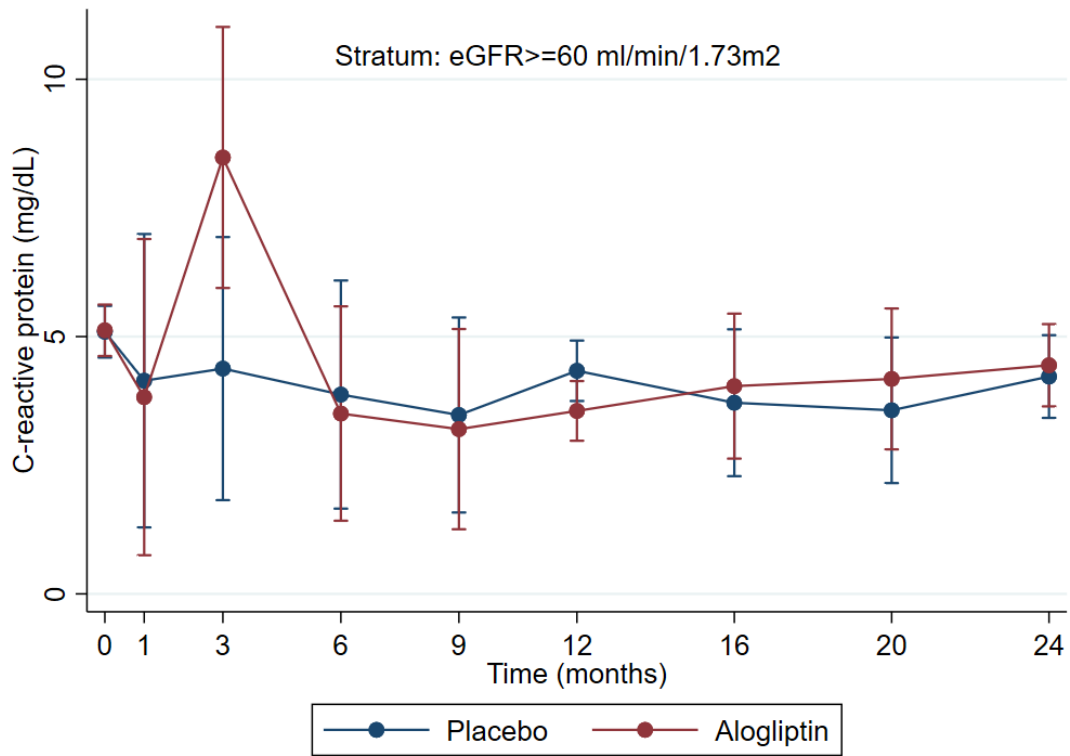
(I) eGFR



(J) UACR



(K) C-reactive protein



P-value > 0.05 for all comparisons (multiple comparison adjusted global effect of alogliptin vs. placebo).

The p-values for each measure within the eGFR strata are:

eGFR ≥ 60:

- Total cholesterol = 0.23
- HDL cholesterol = 0.39

- LDL cholesterol =0.14
- Triglycerides =0.73
- SBP =0.58
- DBP =0.70
- BMI =0.86
- Creatinine =0.62
- eGFR =0.76
- UACR =0.34
- C-reactive protein =0.29

eGFR<60:

- Total cholesterol =0.42
- HDL cholesterol =0.52
- LDL cholesterol =0.84
- Triglycerides =0.24
- SBP =0.61
- DBP =0.86
- BMI =0.67
- Creatinine =0.75
- eGFR =0.54
- UACR =0.76
- C-reactive protein =0.96

Legend: SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.