

## Supplementary file

### Effects of increasing metformin dose vs adding/switching to dipeptidyl peptidase-4 inhibitors on glycemic control in patients with type 2 diabetes

Table S1 Results in each outcome for each quintile of propensity score

(A) Laboratory values in primary study group

PS class	Group	ΔHbA1c, 12 M (%)			ΔHbA1c, 3 M (%)			ΔHbA1c, 6 M (%)		
		Mean	95%CI		Mean	95%CI		Mean	95%CI	
			lower limit	upper limit		lower limit	upper limit		lower limit	upper limit
1	Increased-dose group	-0.89	-1.40	-0.38	-0.91	-1.53	-0.28	-1.11	-1.79	-0.43
	Drug-added group	-1.11	-1.54	-0.67	-1.24	-1.63	-0.85	-1.33	-1.83	-0.83
	Drug-switched group	-0.44	-0.96	0.09	-0.59	-0.74	-0.44	-0.80	-1.32	-0.28
2	Increased-dose group	-1.08	-1.52	-0.64	-1.12	-1.48	-0.76	-1.14	-1.54	-0.74
	Drug-added group	-1.13	-1.53	-0.72	-1.05	-1.38	-0.72	-1.06	-1.41	-0.71
	Drug-switched group	-0.63	-1.40	0.13	-0.83	-1.09	-0.57	-0.70	-0.90	-0.50
3	Increased-dose group	-1.00	-1.37	-0.63	-0.81	-1.08	-0.54	-1.11	-1.46	-0.76
	Drug-added group	-0.98	-1.32	-0.64	-0.99	-1.32	-0.67	-1.11	-1.50	-0.72
	Drug-switched group	-0.50	-0.95	-0.05	-0.32	-0.84	0.20	-0.66	-1.24	-0.07
4	Increased-dose group	-0.99	-1.19	-0.78	-0.80	-0.99	-0.61	-1.04	-1.27	-0.81
	Drug-added group	-0.91	-1.35	-0.47	-0.88	-1.35	-0.41	-0.94	-1.55	-0.32
	Drug-switched group	1.30	-0.66	3.26						
5	Increased-dose group	-0.70	-1.02	-0.38	-0.72	-0.93	-0.50	-0.78	-1.06	-0.51
	Drug-added group	-1.12	-1.66	-0.57	-1.17	-1.67	-0.67	-0.92	-1.42	-0.42
	Drug-switched group	0.50			-0.30			0.00		

The changes in values at 3 months ( $\pm 1$  months) (3 M), 6 months ( $\pm 1$  months) (6 M), and 12 months ( $\pm 3$  months) (12 M) from baseline are indicated using delta ( $\Delta$ ). CI: confidence intervals, Hb: hemoglobin.

PS class	Group	ΔHDL-C (mg/dl)			ΔLDL-C (mg/dl)			ΔTotal-C (mg/dl)			ΔTG (mg/dl)		
		Mean	95%CI		Mean	95%CI		Mean	95%CI		Mean	95%CI	
			lower limit	upper limit		lower limit	upper limit		lower limit	upper limit		lower limit	upper limit
1	Increased-dose group	-2.79	-10.17	4.60	-8.71	-25.59	8.18	-16.73	-34.16	0.71	-24.75	-67.83	18.33
	Drug-added group	1.30	-1.02	3.61	-6.28	-13.15	0.58	-11.74	-19.44	-4.03	-7.49	-34.43	19.45
	Drug-switched group	0.00	-9.02	9.02	-34.80	-76.96	7.36	-20.67	-58.26	16.93	1.86	-49.14	52.86
2	Increased-dose group	0.32	-1.98	2.61	-6.44	-22.84	9.96	-7.47	-25.15	10.21	-34.38	-86.95	18.20
	Drug-added group	-1.24	-3.29	0.82	-15.49	-26.72	-4.26	-16.64	-31.28	-2.00	-19.36	-48.54	9.83
	Drug-switched group	7.20	3.39	11.01	-3.10	-20.82	14.62	-14.00	-24.06	-3.94	-53.50	-135.67	28.67
3	Increased-dose group	0.49	-1.81	2.78	-9.96	-22.74	2.83	-16.00	-29.50	-2.50	4.91	-25.65	35.47
	Drug-added group	0.01	-2.72	2.74	4.35	-5.77	14.47	-1.50	-13.80	10.80	-25.59	-51.13	-0.05
	Drug-switched group	2.28	-8.20	12.77	-9.20	-23.86	5.46	-29.00	-57.69	-0.31	-10.40	-68.81	48.01
4	Increased-dose group	1.50	-0.42	3.42	-5.57	-11.31	0.17	-14.35	-27.38	-1.31	-13.89	-34.19	6.41
	Drug-added group	-0.01	-3.23	3.20	-12.10	-28.16	3.95	2.35	-24.66	29.36	59.80	-139.35	258.95
	Drug-switched group	-4.50	-9.40	0.40	15.50	14.52	16.48	20.00			202.00	-21.44	425.44
5	Increased-dose group	1.51	-0.56	3.58	-10.01	-19.56	-0.46	-16.26	-28.42	-4.09	-39.69	-78.00	-1.37
	Drug-added group	2.05	-1.30	5.40	-17.09	-33.70	-0.47	-27.94	-49.96	-5.92	-65.27	-134.00	3.46
	Drug-switched group	-14.00			-90.00			59.00			1672.00		

The changes in values at 12 months ( $\pm 3$  months) from baseline are indicated using delta ( $\Delta$ ). CI: confidence intervals, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, Total-C: total cholesterol, TG: triglyceride.

PS class	Group	ΔAST (U/L)			ΔALT (U/L)			ΔeGFR (ml/min/1.73m <sup>2</sup> )		
		Mean	95%CI		Mean	95%CI		Mean	95%CI	
			lower limit	upper limit		lower limit	upper limit		lower limit	upper limit
1	Increased-dose group	-8.59	-22.46	5.28	-7.41	-16.63	1.81	0.39	-5.55	6.33
	Drug-added group	-1.58	-6.23	3.06	-2.55	-6.28	1.19	-3.87	-6.34	-1.40
	Drug-switched group	-5.50	-16.39	5.39	-10.70	-20.98	-0.42	1.29	-3.56	6.15
2	Increased-dose group	-7.19	-14.21	-0.16	-6.66	-13.60	0.28	-1.13	-3.53	1.26
	Drug-added group	-1.67	-5.44	2.10	-6.55	-10.71	-2.38	-4.38	-7.02	-1.74
	Drug-switched group	-3.67	-12.26	4.93	-7.17	-19.02	4.68	6.34	-7.70	20.38
3	Increased-dose group	-1.34	-4.77	2.08	-0.84	-5.89	4.21	-1.08	-4.68	2.52
	Drug-added group	-1.78	-6.22	2.66	-5.39	-13.17	2.39	0.58	-4.76	5.93
	Drug-switched group	0.86	-2.98	4.69	-2.14	-6.53	2.25	-1.08	-10.33	8.18
4	Increased-dose group	-2.68	-7.35	1.98	-4.23	-10.23	1.77	-0.81	-3.54	1.92
	Drug-added group	-2.85	-11.77	6.07	-3.09	-11.73	5.54	-9.21	-15.02	-3.39
	Drug-switched group	-4.00	-11.84	3.84	-6.00	-13.84	1.84	-24.40	-41.26	-7.54
5	Increased-dose group	0.03	-3.50	3.56	-2.37	-10.04	5.30	-2.19	-5.21	0.83
	Drug-added group	-8.16	-12.92	-3.40	-15.32	-24.69	-5.95	-7.54	-13.02	-2.07
	Drug-switched group	74.00			51.00			10.20		

The changes in values at 12 months ( $\pm$  3 months) from baseline are indicated using delta ( $\Delta$ ). AST: aspartate aminotransferase, ALT: alanine aminotransferase, CI: confidence intervals, eGFR: estimated glomerular filtration.

(B) Percentage of patients achieving target HbA1c levels, hospitalization, and incidence rate of hypoglycemia in primary study group

PS class	Group	N	HbA1c <6.5% (%)			HbA1c <7.0% (%)			Hospitalization (%)			Incidence rate of hypoglycemia (%)		
			%	95%CI		%	95%CI		%	95%CI		%	95%CI	
				lower limit	upper limit		lower limit	upper limit		lower limit	upper limit		lower limit	upper limit
1	Increased-dose group	17	58.82%	32.92%	81.56%	76.47%	50.10%	93.19%	82.35%	45.02%	138.17%	0.00%		19.51%
	Drug-added group	70	32.86%	22.09%	45.12%	54.29%	41.94%	66.26%	40.00%	26.58%	57.81%	0.00%		5.13%
	Drug-switched group	11	36.36%	10.93%	69.21%	72.73%	39.03%	93.98%	90.91%	43.59%	167.19%	0.00%		28.49%
2	Increased-dose group	34	26.47%	12.88%	44.36%	61.76%	43.56%	77.83%	23.53%	10.16%	46.36%	0.00%		10.28%
	Drug-added group	59	42.37%	29.61%	55.93%	69.49%	56.13%	80.81%	44.07%	28.79%	64.57%	0.00%		6.06%
	Drug-switched group	6	50.00%	11.81%	88.19%	83.33%	35.88%	99.58%	100.00%	36.70%	217.66%	0.00%		45.93%
3	Increased-dose group	40	37.50%	22.73%	54.20%	70.00%	53.47%	83.44%	20.00%	8.63%	39.41%	0.00%		8.81%
	Drug-added group	51	29.41%	17.49%	43.83%	60.78%	46.11%	74.16%	15.69%	6.77%	30.91%	0.00%		6.98%
	Drug-switched group	8	12.50%	0.32%	52.65%	37.50%	8.52%	75.51%	12.50%	0.32%	69.65%	0.00%		36.94%
4	Increased-dose group	63	26.98%	16.57%	39.65%	60.32%	47.20%	72.43%	7.94%	2.58%	18.52%	0.00%		5.69%
	Drug-added group	34	35.29%	19.75%	53.51%	58.82%	40.70%	75.35%	35.29%	18.24%	61.65%	0.00%		10.28%
	Drug-switched group	2	0.00%		84.19%	0.00%		84.19%	0.00%		184.44%	0.00%		84.19%
5	Increased-dose group	72	33.33%	22.66%	45.43%	59.72%	47.50%	71.12%	11.11%	4.80%	21.89%	0.00%		4.99%
	Drug-added group	26	46.15%	26.59%	66.63%	73.08%	52.21%	88.43%	23.08%	8.47%	50.23%	0.00%		13.23%
	Drug-switched group	1	0.00%		97.50%	0.00%		97.50%	0.00%		368.89%	0.00%		97.50%

CI: confidence intervals. Color indicates the relative order in the column as the following sequence: red is the highest; green is the lowest; and intermediate color is the in-between with the ranking corresponding to gradational change of the color from green to red.

(C) Laboratory values in secondary study group

PS class	Group	ΔHbA1c, 12 M (%)			ΔHbA1c, 3 M (%)			ΔHbA1c, 6 M (%)		
		Mean	95%CI		Mean	95%CI		Mean	95%CI	
			lower limit	upper limit		lower limit	upper limit		lower limit	upper limit
1	Increased-dose group	-1.04	-2.09	0.01	-1.30	-2.66	0.06	-1.58	-2.93	-0.24
	Drug-added group	-0.49	-0.79	-0.19	-0.75	-0.98	-0.52	-0.71	-1.05	-0.37
	Drug-switched group	-0.63	-1.15	-0.12	-0.53	-0.81	-0.24	-0.37	-0.94	0.20
2	Increased-dose group	-0.86	-1.12	-0.60	-0.97	-1.34	-0.61	-0.86	-1.18	-0.54
	Drug-added group	-0.52	-0.80	-0.24	-0.74	-0.97	-0.51	-0.58	-0.85	-0.31
	Drug-switched group	-0.50	-0.70	-0.30	-0.65	-0.75	-0.55	-0.85	-1.34	-0.36
3	Increased-dose group	-0.90	-1.30	-0.50	-0.81	-1.12	-0.50	-0.86	-1.27	-0.45
	Drug-added group	-0.70	-1.15	-0.26	-0.88	-1.32	-0.44	-0.97	-1.49	-0.45
	Drug-switched group	0.23	-0.24	0.70	-0.17	-0.86	0.52	-0.20	-0.40	0.00
4	Increased-dose group	-0.44	-0.63	-0.24	-0.52	-0.71	-0.33	-0.69	-0.95	-0.42
	Drug-added group	-0.86	-1.25	-0.47	-0.85	-1.25	-0.45	-0.71	-1.21	-0.21
	Drug-switched group	-0.65	-2.51	1.21				-1.20		
5	Increased-dose group	-1.02	-1.39	-0.65	-0.98	-1.28	-0.67	-1.22	-1.62	-0.83
	Drug-added group	-1.06	-1.66	-0.46	-1.32	-1.98	-0.65	-1.35	-2.07	-0.63
	Drug-switched group	0.50			-0.30			0.00		

The changes in values at 3 months (± 1 months) (3 M), 6 months (± 1 months) (6 M), and 12 months (± 3 months) (12 M) from baseline are indicated using delta (Δ). CI: confidence intervals, Hb: hemoglobin.

PS class	Group	ΔHDL-C (mg/dl)			ΔLDL-C (mg/dl)			ΔTotal-C (mg/dl)			ΔTG (mg/dl)		
		Mean	95%CI		Mean	95%CI		Mean	95%CI		Mean	95%CI	
			lower limit	upper limit		lower limit	upper limit		lower limit	upper limit		lower limit	upper limit
1	Increased-dose group	-2.57	-14.01	8.87	-24.20	-65.70	17.30	-6.50	-31.88	18.88	-39.29	-121.01	42.44
	Drug-added group	-0.54	-3.08	1.99	-6.03	-14.65	2.60	-10.29	-19.93	-0.65	6.28	-19.61	32.17
	Drug-switched group	2.67	-7.60	12.93	-24.50	-35.28	-13.72	-13.33	-30.47	3.80	-15.67	-72.81	41.48
2	Increased-dose group	3.24	-1.05	7.54	-3.36	-16.15	9.44	-18.00	-44.62	8.62	-16.73	-47.98	14.52
	Drug-added group	0.09	-1.91	2.09	-8.23	-19.28	2.81	-6.00	-16.53	4.53	-38.68	-72.57	-4.79
	Drug-switched group	2.00	-3.88	7.88	-24.50	-66.64	17.64	-58.00			-15.00	-124.76	94.76
3	Increased-dose group	-1.12	-3.84	1.59	-19.61	-29.38	-9.84	-18.92	-32.57	-5.26	-42.35	-114.67	29.96
	Drug-added group	1.27	-1.47	4.01	-12.57	-24.47	-0.67	-8.93	-26.51	8.64	-14.96	-33.37	3.45
	Drug-switched group	4.30	3.71	4.89	0.80	-4.69	6.29	-11.00	-11.00	-11.00	-109.00	-222.68	4.68
4	Increased-dose group	-0.85	-3.72	2.01	-7.66	-14.56	-0.77	-11.89	-23.36	-0.42	2.42	-24.53	29.37
	Drug-added group	-0.85	-3.95	2.25	-10.55	-22.80	1.70	-16.95	-31.54	-2.37	-34.73	-91.16	21.70
	Drug-switched group	-7.15	-17.24	2.94	16.00			-19.00	-95.44	57.44	82.50	71.72	93.28
5	Increased-dose group	2.19	-0.02	4.41	-9.45	-21.57	2.68	-12.96	-29.82	3.91	-5.88	-32.91	21.14
	Drug-added group	2.77	-3.75	9.29	-14.14	-36.15	7.86	5.42	-37.55	48.39	127.33	-265.27	519.93
	Drug-switched group	-14.00			-90.00			59.00			1672.00		

The changes in values at 12 months ( $\pm$  3 months) from baseline are indicated using delta ( $\Delta$ ). CI: confidence intervals, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, Total-C: total cholesterol, TG: triglyceride.

PS class	Group	ΔAST (U/L)			ΔALT (U/L)			ΔeGFR (ml/min/1.73m <sup>2</sup> )		
		Mean	95%CI		Mean	95%CI		Mean	95%CI	
			lower limit	upper limit		lower limit	upper limit		lower limit	upper limit
1	Increased-dose group	-14.00	-43.22	15.22	-12.88	-29.43	3.68	2.44	-7.15	12.03
	Drug-added group	-1.72	-8.56	5.12	-3.00	-8.04	2.04	-2.30	-4.70	0.11
	Drug-switched group	-7.80	-17.51	1.91	-11.80	-20.08	-3.52	-7.60	-13.35	-1.85
2	Increased-dose group	-11.09	-28.95	6.77	-8.55	-23.88	6.79	-2.83	-6.30	0.64
	Drug-added group	-3.45	-8.27	1.36	-9.26	-17.89	-0.63	-3.92	-7.07	-0.76
	Drug-switched group	-22.50	-66.60	21.60	-25.00	-70.08	20.08	-8.51	-36.95	19.93
3	Increased-dose group	-8.76	-16.98	-0.54	-10.14	-20.23	-0.05	2.28	-0.88	5.45
	Drug-added group	-3.73	-9.94	2.48	-5.03	-12.18	2.11	1.04	-7.23	9.31
	Drug-switched group	-3.00	-6.39	0.39	-7.00	-11.08	-2.92	8.07	3.41	12.72
4	Increased-dose group	0.19	-3.92	4.30	1.76	-5.62	9.14	0.23	-3.39	3.84
	Drug-added group	-2.90	-7.15	1.35	-5.90	-14.00	2.20	-5.41	-9.25	-1.57
	Drug-switched group	-4.50	-11.36	2.36	-8.00	-11.92	-4.08	-8.28	-23.02	6.47
5	Increased-dose group	3.21	-1.77	8.18	3.51	-6.85	13.88	-1.97	-5.20	1.26
	Drug-added group	-0.78	-13.46	11.91	-6.72	-19.41	5.96	-4.37	-9.79	1.04
	Drug-switched group	74.00			51.00			10.20		

The changes in values at 12 months ( $\pm$  3 months) from baseline are indicated using delta ( $\Delta$ ). AST: aspartate aminotransferase, ALT: alanine aminotransferase, CI: confidence intervals, eGFR: estimated glomerular filtration.

(D) Percentage of patients achieving target HbA1c levels, hospitalization, and incidence rate of hypoglycemia in secondary study group

PS class	Group	N	HbA1c <6.5% (%)			HbA1c <7.0% (%)			Hospitalization (%)			Incidence rate of hypoglycemia (%)		
			%	95%CI		%	95%CI		%	95%CI		%	95%CI	
				lower limit	upper limit		lower limit	upper limit		lower limit	upper limit		lower limit	upper limit
1	Increased-dose group	8	37.50%	8.52%	75.51%	75.00%	34.91%	96.81%	112.50%	51.44%	213.56%	0.00%		36.94%
	Drug-added group	44	36.36%	22.41%	52.23%	61.36%	45.50%	75.64%	11.36%	3.69%	26.52%	0.00%		8.04%
	Drug-switched group	6	83.33%	35.88%	99.58%	83.33%	35.88%	99.58%	133.33%	57.56%	262.72%	0.00%		45.93%
2	Increased-dose group	12	33.33%	9.92%	65.11%	100.00%	73.54%		16.67%	2.02%	60.21%	0.00%		26.46%
	Drug-added group	44	25.00%	13.19%	40.34%	61.36%	45.50%	75.64%	27.27%	14.09%	47.64%	0.00%		8.04%
	Drug-switched group	2	0.00%		84.19%	0.00%		84.19%	0.00%		184.44%	0.00%		84.19%
3	Increased-dose group	23	21.74%	7.46%	43.70%	52.17%	30.59%	73.18%	26.09%	9.57%	56.78%	0.00%		14.82%
	Drug-added group	32	31.25%	16.12%	50.01%	62.50%	43.69%	78.90%	12.50%	3.41%	32.00%	0.00%		10.89%
	Drug-switched group	3	0.00%		70.76%	0.00%		70.76%	0.00%		122.96%	0.00%		70.76%
4	Increased-dose group	24	33.33%	15.63%	55.32%	54.17%	32.82%	74.45%	0.00%		15.37%	0.00%		14.25%
	Drug-added group	32	37.50%	21.10%	56.31%	71.88%	53.25%	86.25%	15.63%	5.07%	36.46%	0.00%		10.89%
	Drug-switched group	2	0.00%		84.19%	0.00%		84.19%	0.00%		184.44%	0.00%		84.19%
5	Increased-dose group	39	28.21%	15.00%	44.87%	64.10%	47.18%	78.80%	7.69%	1.59%	22.48%	0.00%		9.03%
	Drug-added group	19	42.11%	20.25%	66.50%	68.42%	43.45%	87.42%	10.53%	1.27%	38.02%	0.00%		17.65%
	Drug-switched group	1	0.00%		97.50%	0.00%		97.50%	0.00%		368.89%	0.00%		97.50%

CI: confidence intervals. Color indicates the relative order in the column as the following sequence: red is the highest; green is the lowest; and intermediate color is the in-between with the ranking corresponding to gradational change of the color from green to red.



Table S2 The changes in eGFR values at 12 months ( $\pm 3$  months) from baseline in each class of baseline eGFR value in primary study group

	Increased-dose group			Drug-added group			Drug-switched group		
	Mean	95%CI1		Mean	95%CI		Mean	95%CI	
		lower limit	upper limit		lower limit	upper limit		lower limit	upper limit
eGFR(0) <45	-0.832	-121.046	119.382	-2.076	-4.970	0.817	-6.350	-23.405	10.704
45 $\leq$ eGFR(0) <60	0.605	0.139	1.070	0.540	-3.319	4.399	3.967	-11.953	19.888
60 $\leq$ eGFR(0) <90	-0.483	-1.610	0.644	-3.703	-5.586	-1.820	-4.230	-42.995	34.534
eGFR(0) $\geq$ 90	-3.437	-8.677	1.804	-10.578	-29.182	8.025	-6.519	-33.173	20.136

CI: confidence intervals, eGFR: estimated glomerular filtration. eGFR(0): eGFR value (ml/min/1.73m<sup>2</sup>) during the baseline. Orange color indicates that both the values of 95% CI upper limit and lower limit are positive, and blue color indicates that both are negative.