

Appendix Table 1. Baseline characteristics in groups of patients treated with metformin only, insulin only, or other OHA only, applied in Cox regression analyses presented in Table 3.

	Metformin Only	Insulin only	Other OHA only	P metformin only/ insulin only Unadjusted	P metformin only/ insulin only Adjusted for PS	P metformin only/ other OHA only Unadjusted	P metformin only/ other OHA only Adjusted for PS
N	14697	12291	5171				
Age (Years)	63.8 (9.7)	65.2 (10.5)	69.7 (9.5)	<0.001	0.49	<0.001	0.126
HbA1c (%)	6.9 (3.1)	7.6 (3.4)	6.9 (3.0)	<0.001	0.46	0.002	0.24
Systolic blood pressure (mmHg)	139.4 (16.6)	138.9 (18.0)	141.4 (17.5)	0.018	0.96	<0.001	0.164
Diabetes duration (Years)	4.6 (4.3)	14.3 (10.4)	7.5 (6.2)	<0.001	0.78	<0.001	0.37
eGFR (mL/min/1.73 m ²)	82.0 (20.2)	73.6 (23.8)	73.8 (21.1)	<0.001	0.94	<0.001	0.177
BMI (Kg/m ²)	30.7 (4.9)	27.4 (4.8)	27.2 (4.5)	<0.001	0.53	<0.001	0.008
Non-HDL-C (mmol/L)	3.64 (1.00)	3.35 (0.98)	3.60 (0.99)	<0.001	0.78	0.008	0.62
Microalbuminuria	21.0%	30.8%	24.2%	<0.001	0.46	<0.001	0.50
Previous hospitalisation	11.5%	23.1%	15.5%	<0.001	0.57	<0.001	0.73
Female sex	44.7%	40.2%	39.2%	<0.001	0.73	<0.001	0.59
History of CVD	15.9%	26.4%	21.4%	<0.001	0.97	<0.001	0.111
History of CHF	3.5%	8.9%	6.4%	<0.001	0.022	<0.001	0.74
History of serious infections	1.8%	4.9%	2.8%	<0.001	0.96	<0.001	0.72
Cardiac glycosides	2.6%	3.0%	4.3%	0.064	0.96	<0.001	0.196
Organic nitrates	6.3%	8.5%	8.8%	<0.001	0.61	<0.001	0.45
Acetylsalicylic Acid	45.4%	45.7%	45.9%	0.56	0.58	0.52	0.65
Lipid modifying agents	49.9%	44.8%	44.1%	<0.001	0.88	<0.001	0.94
Antihypertensive agents	71.8%	66.2%	71.3%	<0.001	0.38	0.58	0.81
Multi-dose dispensation	1.4%	3.0%	1.5%	<0.001	0.97	0.54	0.97
Smoker	14.8%	14.9%	12.3%	0.77	0.104	<0.001	0.28

Means ± standard deviation (SD) and proportions (%) of clinical variables at baseline. P values are given for comparison between metformin only and insulin only, and between metformin only and other OHA only, unadjusted and after adjustment by stratification for octiles of propensity scores applied for each comparison.

Appendix Table 2: Time of exposure (months) to specific glucose-lowering agents, and proportions changing treatment (%) in each group.

	Metformin Only	Metformin + other OHA	Metformin + insulin	Insulin only	Other OHA only	Insulin + other OHA	Metformin + insulin + other OHA
Mean Exposure time to metformin	49,4	51,0	46,3				48,9
Mean Exposure time to insulin			51,8	55,3		54,1	53,4
Mean Exposure time to Other Oral		49,1			45,3	39,5	48,3
Change treatment (%)	80.8 %	80.5 %	81.8 %	91.3 %	88.4 %	56.5 %	93.9 %

Appendix Table 3: Numbers and frequencies (%) of endpoint events in each treatment group.

	Metformin Only	Metformin + other OHA	Metformin + insulin	Insulin only	Other OHA only	Insulin + other OHA	Metformin+ insulin + other OHA
Any CVD	1734 (3.3%)	1287 (4%)	1338 (5.4%)	2389 (5.9%)	929 (5.2%)	334 (7.8%)	415 (5.4%)
Fatal CVD	264 (0.5%)	230 (0.6%)	276 (1%)	681 (1.4%)	237 (1.2%)	94 (1.8%)	74 (0.8%)
Acidosis/serious infection	1154 (2.1%)	843 (2.5%)	899 (3.4%)	1867 (4.3%)	623 (3.3%)	235 (5%)	259 (3.1%)
Fatal acidosis/serious infection	127 (0.2%)	95 (0.3%)	124 (0.4%)	325 (0.7%)	109 (0.5%)	41 (0.8%)	29 (0.3%)
All-cause mortality	971 (1.7%)	834 (2.4%)	818 (2.9%)	2002 (4.2%)	745 (3.7%)	258 (4.9%)	250 (2.8%)

Appendix Table 4. Adjusted hazard ratios (HR) with 95% confidence intervals (CI) for any CVD, fatal CVD, any acidosis/serious infection, fatal acidosis/serious infection, and all-cause mortality in all patients, in each treatment group, and with other OHA only as reference

	Other OHA only	Insulin Only	Metformin only	Insulin + other OHA	Metformin + other OHA	Metformin + insulin	Metformin + insulin + other OHA
Any CVD	Reference	1.13 (1.04-1.22)	0.88 (0.81-0.96)	1.24 (1.09-1.41)	0.98 (0.9-1.07)	1.12 (1.03-1.23)	1.17 (1.04-1.32)
Fatal CVD	Reference	1.09 (0.92-1.28)	0.77 (0.64-0.93)	0.91 (0.7-1.16)	*	*	0.93 (0.71-1.22)
Any acidosis/serious infection	Reference	1.19 (1.08-1.31)	0.87 (0.78-0.96)	1.14 (0.97-1.32)	0.9 (0.81-1)	1.04 (0.93-1.16)	1 (0.86-1.16)
Fatal acidosis/serious infection	Reference	1.27 (1.01-1.62)	0.78 (0.6-1.02)	1.03 (0.71-1.48)	0.73 (0.55-0.97)	1.1 (0.83-1.45)	0.88 (0.57-1.32)
All-cause mortality	Reference	1.12 (1.02-1.23)	0.76 (0.69-0.84)	0.99 (0.85-1.14)	0.88 (0.8-0.98)	0.96 (0.86-1.07)	1.01 (0.86-1.17)

*Non-proportional hazards, group excluded from analysis.

Adjustments were made for age, sex, diabetes duration, HbA1c, non-HDL-C, BMI, smoking, eGFR, multi-dose dispensation, previous hospitalisation, history of CVD and CHF, microalbuminuria, and treatment with antihypertensive agents, lipid lowering agents and cardiac glycosides.

Appendix Table 5. Adjusted hazard ratios with 95 % confidence intervals for any CVD, fatal CVD, any acidosis/serious infection, fatal acidosis/serious infection, and all-cause mortality in patients with SU only and patients with metformin only as reference

	SU only	Metformin Only	SU only Vs Metformin only
	Events/Patients N/N	Events/Patients N/N	Hazard ratio (95% CI) P-value
Any CVD	788 / 4084	1734 / 14317	0.99 (0.89-1.09) 0.82
Fatal CVD	210 / 4272	264 / 14696	1.01 (0.82-1.25) 0.91
Any acidosis/serious infection	506 / 4178	1154 / 14517	1.0 (0.89-1.14) 0.96
Fatal acidosis/serious infection	94 / 4272	127 / 14697	1.17 (0.85-1.60) 0.34
All-cause mortality	664 / 4272	971 / 14697	1.15 (1.02-1.30) 0.019

Adjusted by stratification with octiles of propensity scores.

Appendix Table 6. Adjusted hazard ratios (HR) with 95% confidence intervals (CI) and p-values for any CVD, fatal CVD, any acidosis/serious infection, fatal acidosis/serious infection, and all-cause mortality in patients treated with insulin + other OHA or insulin + metformin, and with insulin only as reference

	Insulin only		Insulin + other OHA		Insulin + metformin	
	Reference	HR (95% CI)	HR (95% CI)	P-value	HR (95% CI)	P-value
Any CVD	Reference	1.10 (0.98-1.23)	1.10 (0.98-1.23)	0.1154	0.96 (0.89-1.03)	0.2823
Fatal CVD	Reference	0.84 (0.67-1.05)	0.84 (0.67-1.05)	0.1334	0.90 (0.77-1.05)	0.1687
Any acidosis/serious infection	Reference	0.96 (0.84-1.1)	0.96 (0.84-1.1)	0.5976	0.86 (0.79-0.94)	0.0007
Fatal acidosis/serious infection	Reference	0.82 (0.58-1.13)	0.82 (0.58-1.13)	0.2413	0.85 (0.68-1.06)	0.1532
All-cause mortality	Reference	0.89 (0.78-1.01)	0.89 (0.78-1.01)	0.0766	0.84 (0.76-0.91)	<.0001

Adjustments were made for age, sex, diabetes duration, HbA1c, non-HDL-C, BMI, smoking, eGFR, multi-dose dispensation, previous hospitalisation, history of CVD and CHF, microalbuminuria, and treatment with antihypertensive agents, lipid lowering agents and cardiac glycosides.