

Supplementary Table 1. Unadjusted baseline data in an additional large study group comparing patients with metformin and sulphonylurea, or comparing patients with metformin and meglitinide.

	Metformin	SU	Meglitinide	P value metformin/ SU unadjusted	P value metformin/ meglitinide unadjusted
Age	63.8±11.1 (64207)	70.4±11.3 (4568)	68.7±12.1 (892)	<0.001	<0.001
Females	41.9 (64207)	39.1 (4568)	34.9 (892)	<0.001	<0.001
Diabetes duration	2.3±3.5 (56292)	3.8±4.8 (3876)	3.3±4.4 (791)	<0.001	<0.001
Previous CVD	13.8 (64207)	18.9 (4568)	15.6 (892)	<0.001	0.1
Previous CHF	3.1 (64207)	7.3 (4568)	7.9 (892)	<0.001	<0.001
Atrial fibrillation	5.2 (64207)	9.7 (4568)	9.9 (892)	<0.001	<0.001
Education score 1-3	1.82±0.72 (62703)	1.71±0.73 (4288)	1.74±0.74 (844)	<0.001	0.002
Psychiatric drugs	25.4 (64207)	23.8 (4568)	22.7 (892)	0.02	0.06
Multidose	1.7 (62703)	3.8 (4288)	0.8 (892)	<0.001	0.04

Means ± SD or frequencies (%) are given, with numbers in parenthesis. Significance levels comparing two groups using student's t-test or χ^2 -test.

Abbreviations: CVD: cardiovascular disease; CHF: congestive heart failure; multidose: multidose drug dispensing.

Supplementary table 2. Adjusted hazard ratios for monotherapy failures with sulphonylurea (n=1026) versus metformin (n=16061), and with meglitinide (n=222) versus metformin, using two adjustment models, and using a propensity score for each comparison.

Therapy failure	Drugs	Events N (%)	Model 1	P	Model 2	P
			HR (95% CI)	value	HR (95% CI)	value
Overall	SU	543 (52.9)	1.59 (1.45-1.75)	<0.001	1.52 (1.38-1.67)	<0.001
	Metformin	5980 (37.2)	1.0		1.0	
Add on	SU	271 (26.4)	2.78 (2.42-3.18)	<0.001	2.54 (2.21-2.92)	<0.001
	Metformin	1987 (12.4)	1.0		1.0	
Switch	SU	72 (7.0)	2.17 (1.65-2.86)	<0.001	2.42 (1.84-3.17)	<0.001
	Metformin	399 (2.5)	1.0		1.0	
Add on + switch	SU	343 (33.4)	2.71 (2.39-3.06)	<0.001	2.51 (2.22-2.85)	<0.001
	Metformin	2386 (14.9)	1.0		1.0	
Discontinuation	SU	200 (19.5)	0.94 (0.81-1.09)	0.4	0.90 (0.78-1.05)	0.2
	Metformin	3594 (22.4)	1.0		1.0	
Overall	Meglitinide	139 (62.6)	1.74 (1.47-2.07)	<0.001	1.64 (1.38-1.95)	<0.001
	Metformin	5980 (37.2)	1.0		1.0	
Add on	Meglitinide.	66 (29.7)	2.75 (2.14-3.53)	<0.001	2.35 (1.83-3.02)	<0.001
	Metformin	1987 (12.4)	1.0		1.0	
Switch	Meglitinide	24 (10.8)	3.13 (2.04-4.79)	<0.001	4.09 (2.68-6.26)	<0.001
	Metformin	399 (2.5)	1.0		1.0	
Add on + switch	Meglitinide.	90 (40.5)	2.93 (2.36-3.63)	<0.001	2.65 (2.14-3.29)	<0.001
	Metformin	2386 (14.9)	1.0		1.0	
Discontinuation	Meglitinide.	49 (22.1)	1.00 (0.75-1.33)	0.9	0.97 (0.73-1.28)	0.8
	Metformin	3594 (22.4)	1.0		1.0	

Model 1: covariate adjustment for age, sex, diabetes duration, index HbA1c, index BMI, index eGFR, delta eGFR, previous cardiovascular disease, congestive heart failure and atrial fibrillation, educational level, use of psychiatric medications, and multi-dose drug dispensing.

Model 2: adjusting with five strata of a propensity score for each comparison including all covariates in Model 1 and index year.

Abbreviations: HR: hazard ratio; CI: confidence interval.

Supplementary Table 3. Adjusted hazard ratios for monotherapy failures in patients with sulphonylurea (n=3654) versus metformin (n=55087), and with meglitinide (n=754) versus metformin, using patients with data available for all included covariate variables.

Monotherapy failure	Drugs	Events N (%)	HR (95% CI)	P value
Overall	SU	2223 (60.8)	1.64 (1.57-1.72)	<0.001
	Metformin	24453 (44.4)	1.0	
Add on	SU	1120 (30.7)	2.72 (2.55-2.90)	<0.001
	Metformin	8434 (15.3)	1.0	
Switch	SU	326 (8.9)	3.65 (3.21-4.14)	<0.001
	Metformin	1356 (2.5)	1.0	
Add on + switch	SU	1446 (39.6)	2.90 (2.74-3.07)	<0.001
	Metformin	9790 (17.8)	1.0	
Discontinuation	SU	777 (21.3)	0.90 (0.84-0.97)	0.005
	Metformin	14663 (26.6)	1.0	
Overall	Meglitinide	502 (66.6)	1.73 (1.58-1.89)	<0.001
	Metformin	24453 (44.4)	1.0	
Add on	Meglitinide	249 (33.0)	2.64 (2.33-2.99)	<0.001
	Metformin	8434 (15.3)	1.0	
Switch	Meglitinide	90 (11.9)	4.71 (3.79-5.84)	<0.001
	Metformin	1356 (2.5)	1.0	
Add on + switch	Meglitinide	339 (45.0)	3.02 (2.71-3.37)	<0.001
	Metformin	9790 (17.8)	1.0	
Discontinuation	Meglitinide	163 (21.6)	0.90 (0.78-1.06)	0.2
	Metformin	14663 (26.6)	1.0	

Covariate adjustment for age, sex, diabetes duration, previous cardiovascular disease, congestive heart failure and atrial fibrillation, educational level, use of psychiatric medications, and multi-dose drug dispensing. Abbreviations: HR: hazard ratio; CI: confidence interval.

Supplementary Table 4. Quantified effects of hypothetical unmeasured and/or unknown confounders in the propensity score matched cohort with metformin users or sulphonylurea (SU) users.

We assigned a hypothetical binary confounder a hazard ratio (HR), for all outcomes listed below, of 2.0 and assessed the HR associated with SU compared with metformin given different prevalence of this confounder in the two groups. The table shows HRs with 95% confidence intervals after adjustment for the binary confounder.

Monotherapy failure		P (confounder) ¹ metformin users			
		0.0	0.2	0.4	
Overall	P (confounder) ¹ for SU users	0.0	1.74 (1.56-1.94)		
		0.2	1.45 (1.30-1.62)	1.74 (1.56-1.94)	
		0.4	1.24 (1.11-1.39)	1.49 (1.34-1.66)	1.74 (1.56-1.94)
		0.6	1.09 (0.98-1.21)	1.31 (1.17-1.46)	1.52 (1.37-1.70)
		0.8	0.97 (0.87-1.08)	1.16 (1.04-1.29)	1.35 (1.21-1.51)
Add-on	P (confounder) for SU users	0.0	3.14 (2.66-3.69)		
		0.2	2.62 (2.22-3.08)	3.14 (2.66-3.69)	
		0.4	2.24 (1.90-2.64)	2.69 (2.28-3.16)	3.14 (2.66-3.69)
		0.6	1.96 (1.66-2.31)	2.36 (2.00-2.77)	2.75 (2.33-3.23)
		0.8	1.74 (1.48-2.05)	2.09 (1.77-2.46)	2.44 (2.07-2.87)
Switch	P (confounder) for SU users	0.0	2.81 (2.01-3.92)		
		0.2	2.34 (1.68-3.27)	2.81 (2.01-3.92)	
		0.4	2.01 (1.44-2.80)	2.41 (1.72-3.36)	2.81 (2.01-3.92)
		0.6	1.76 (1.26-2.45)	2.11 (1.51-2.94)	2.46 (1.76-3.43)
		0.8	1.56 (1.12-2.18)	1.87 (1.34-2.61)	2.19 (1.56-3.05)
Add-on + switch	P (confounder) for SU users	0.0	3.06 (2.65-3.56)		
		0.2	2.55 (2.21-2.97)	3.06 (2.65-3.56)	
		0.4	2.19 (1.89-2.54)	2.62 (2.27-3.05)	3.06 (2.65-3.56)
		0.6	1.91 (1.66-2.23)	2.30 (1.99-2.67)	2.68 (2.32-3.12)
		0.8	1.70 (1.47-1.98)	2.04 (1.77-2.37)	2.38 (2.06-2.77)
Discontinuation	P (confounder) for SU users	0.0	0.94 (0.79-1.13)		
		0.2	0.78 (0.66-0.94)	0.94 (0.79-1.13)	
		0.4	0.67 (0.56-0.81)	0.81 (0.68-0.97)	0.94 (0.79-1.13)
		0.6	0.59 (0.49-0.71)	0.71 (0.59-0.85)	0.82 (0.69-0.99)
		0.8	0.52 (0.44-0.63)	0.63 (0.53-0.75)	0.73 (0.61-0.88)

¹ P (confounder) is the prevalence of the confounder.

Supplementary Table 5. Quantified effects of hypothetical unmeasured and/or unknown confounders in the propensity score matched cohort with metformin users and meglitinide users.

We assigned a hypothetical binary confounder a hazard ratio (HR), for all outcomes listed below, of 2.0 and assessed the HR associated with meglitinide compared with metformin given different prevalence of this confounder in the two groups. The table shows HRs with 95% confidence intervals after adjustment for the binary confounder.

Monotherapy failure		P (confounder) ¹ metformin users			
		0.0	0.2	0.4	
Overall	P (confounder) ¹ for meglitinide users	0.0	1.66 (1.37-2.00)		
		0.2	1.38 (1.14-1.67)	1.66 (1.37-2.00)	
		0.4	1.19 (0.98-1.43)	1.42 (1.17-1.71)	1.66 (1.37-2.00)
		0.6	1.04 (0.86-1.25)	1.25 (1.03-1.50)	1.45 (1.20-1.75)
		0.8	0.92 (0.76-1.11)	1.11 (0.91-1.33)	1.29 (1.07-1.56)
Add-on	P (confounder) for meglitinide users	0.0	2.52 (1.89-3.37)		
		0.2	2.10 (1.58-2.81)	2.52 (1.89-3.37)	
		0.4	1.80 (1.35-2.41)	2.16 (1.62-2.89)	2.52 (1.89-3.37)
		0.6	1.58 (1.18-2.11)	1.89 (1.42-2.53)	2.21 (1.65-2.95)
		0.8	1.40 (1.05-1.87)	1.68 (1.26-2.25)	1.96 (1.47-2.62)
Switch	P (confounder) for meglitinide users	0.0	3.78 (2.25-6.32)		
		0.2	3.15 (1.88-5.27)	3.78 (2.25-6.32)	
		0.4	2.70 (1.61-4.51)	3.24 (1.93-5.42)	3.78 (2.25-6.32)
		0.6	2.36 (1.41-3.95)	2.84 (1.69-4.74)	3.31 (1.97-5.53)
		0.8	2.10 (1.25-3.51)	2.52 (1.50-4.21)	2.94 (1.75-4.92)
Add-on + switch	P (confounder) for meglitinide users	0.0	2.76 (2.15-3.55)		
		0.2	2.30 (1.79-2.96)	2.76 (2.15-3.55)	
		0.4	1.97 (1.54-2.54)	2.37 (1.84-3.04)	2.76 (2.15-3.55)
		0.6	1.73 (1.34-2.22)	2.07 (1.61-2.66)	2.42 (1.88-3.11)
		0.8	1.53 (1.19-1.97)	1.84 (1.43-2.37)	2.15 (1.67-2.76)
Discontinuation	P (confounder) for meglitinide users	0.0	0.95 (0.70-1.29)		
		0.2	0.79 (0.58-1.08)	0.95 (0.70-1.29)	
		0.4	0.68 (0.50-0.92)	0.81 (0.60-1.11)	0.95 (0.70-1.29)
		0.6	0.59 (0.44-0.81)	0.71 (0.53-0.97)	0.83 (0.61-1.13)
		0.8	0.53 (0.39-0.72)	0.63 (0.47-0.86)	0.74 (0.54-1.00)

¹ P (confounder) is the prevalence of the confounder.

Supplementary figure 1. Cumulative incidence of monotherapy failure in matched samples of meglitinide (n=218) versus metformin (n=1090), when followed for up to 5.5 years. All patients were on continuous treatment for at least 12 months. A: All failure; B. Add on; C. Switch; D. Discontinuation. All graphs with log rank test $p < 0.001$, except D with log-rank test non-significant.

