Web appendix 6: Web tables

Web table 1   Mean values prior to starting different medication combinations

	age	Townsend score	HBA1C mmol/mol	BMI kg/m^2	Cholesterol /HDL ratio	SBP mmHg	Creatinine mol/l
No treatment	64.6	0.4	57.6	30.5	3.9	132.7	87.9
Monotherapy							
Metformin alone	64.1	0.5	60.0	30.8	3.8	132.3	83.2
Sulphonylureas alone	70.5	0.4	63.1	28.8	3.8	132.2	110.8
Insulin alone	66.4	0.3	66.6	29.6	3.9	130.2	118.5
Glitazones alone	66.8	-0.2	59.3	32.0	3.8	133.3	101.4
Gliptins alone	67.8	0.1	63.5	31.2	3.9	131.5	98.3
Other hypoglycaemic treatments alone	63.7	0.7	63.2	32.3	4.0	132.3	100.6
Dual therapy							
Metformin and sulphonylureas	65.5	0.7	65.3	30.3	3.8	132.9	87.7
Metformin and insulin	63.5	0.6	69.4	31.1	3.9	131.7	87.4
Metformin and glitazones	61.2	0.1	63.0	32.6	3.8	132.8	82.5
Metformin and gliptins	61.8	0.3	65.2	32.2	3.8	131.7	80.4
Metformin and other hypoglycaemic	59.3	0.7	66.1	34.1	3.9	131.6	79.6
Sulphonylureas and insulin	70.7	0.3	74.4	29.2	4.0	131.2	134.2
Sulphonylureas and glitazones	70.2	0.1	65.9	31.0	3.8	133.4	112.8
Sulphonylureas and gliptins	70.0	0.2	70.2	30.7	3.9	132.5	105.9
Sulphonylureas and other hypoglycaemic	66.0	0.4	70.6	32.8	4.1	131.4	106.7
Triple therapy							
Metformin, sulphonylureas and insulin	65.0	0.6	76.2	30.3	3.9	132.2	90.8
Metformin, sulphonylureas and glitazones	63.3	0.5	68.2	31.3	3.8	133.3	86.5
Metformin, sulphonylureas and gliptins	63.5	0.7	70.4	31.3	3.8	132.4	83.6
Metformin, sulphonylureas and other hypoglycaemic	60.4	0.8	72.7	33.8	4.0	132.5	81.8
All other drug combinations	61.6	0.5	73.2	32.5	3.9	132.5	86.5

Web table 2. Adjusted hazard ratios (95% CI) for each outcome for different adjusted models (see footnote)

		Adjusted HR model A [±]	Adjusted HR model B [±]	Adjusted HR model D [†]	Adjusted HR model E[±]
Blindness	glitazones[§]	0.77 (0.61 to 0.96)	0.68 (0.55 to 0.86)	0.71 (0.56 to 0.89)	0.82 (0.59 to 1.13)
	gliptins[§]	0.87 (0.72 to 1.05)	0.79 (0.66 to 0.96)	0.83 (0.69 to 1.00)	0.76 (0.58 to 1.00)
	metformin[§]	0.83 (0.78 to 0.89)	0.68 (0.64 to 0.73)	0.70 (0.65 to 0.75)	0.71 (0.66 to 0.77)
	sulphonylureas[§]	1.13 (1.05 to 1.22)	0.94 (0.87 to 1.01)	1.06 (0.96 to 1.16)	1.03 (0.92 to 1.16)
	insulin[§]	1.67 (1.45 to 1.93)	1.38 (1.19 to 1.59)	1.88 (1.60 to 2.20)	1.52 (1.18 to 1.95)
	Other hypoglycaemic [§]	0.96 (0.73 to 1.26)	0.80 (0.61 to 1.06)	0.83 (0.63 to 1.09)	0.93 (0.64 to 1.35)
	insulin*age			0.968 (0.957 to 0.980)	
	Sulphonylureas*age			0.991 (0.985 to 0.997)	
Hyperglycaemia	glitazones[§]	0.91 (0.79 to 1.06)	0.84 (0.72 to 0.98)	0.87 (0.75 to 1.02)	0.82 (0.59 to 1.13)
	gliptins[§]	1.01 (0.89 to 1.14)	0.94 (0.83 to 1.07)	0.93 (0.82 to 1.05)	0.76 (0.58 to 1.00)
	metformin[§]	0.71 (0.68 to 0.74)	0.64 (0.62 to 0.66)	0.65 (0.62 to 0.68)	0.71 (0.66 to 0.77)
	sulphonylureas[§]	1.13 (1.08 to 1.19)	1.05 (1.00 to 1.11)	0.99 (0.94 to 1.04)	1.03 (0.92 to 1.16)
	insulin[§]	1.89 (1.71 to 2.09)	1.81 (1.63 to 2.00)	1.49 (1.33 to 1.68)	1.52 (1.18 to 1.95)
	Other hypoglycaemic [§]	1.07 (0.90 to 1.28)	0.96 (0.80 to 1.14)	0.96 (0.81 to 1.15)	0.93 (0.64 to 1.35)
	insulin*BMI			0.972 (0.956 to 0.988)	
	insulin*HBA1C			1.008 (1.004 to 1.012)	
Hypoglycaemia	glitazones[§]	1.27 (1.14 to 1.41)	1.18 (1.06 to 1.32)	1.16 (1.02 to 1.31)	1.38 (1.14 to 1.67)
	gliptins[§]	0.86 (0.77 to 0.97)	0.82 (0.73 to 0.92)	0.92 (0.82 to 1.03)	0.96 (0.82 to 1.14)
	metformin[§]	0.58 (0.55 to 0.61)	0.55 (0.52 to 0.58)	0.54 (0.51 to 0.57)	0.51 (0.47 to 0.55)
	sulphonylureas[§]	3.26 (3.09 to 3.44)	2.86 (2.71 to 3.01)	2.74 (2.60 to 2.89)	3.99 (3.69 to 4.31)
	insulin[§]	4.90 (4.59 to 5.23)	4.24 (3.97 to 4.53)	4.44 (4.14 to 4.76)	6.07 (5.47 to 6.73)
	Other hypoglycaemic [§]	1.07 (0.92 to 1.24)	0.98 (0.84 to 1.14)	1.11 (0.95 to 1.31)	1.35 (1.09 to 1.67)
	Glitazones*age			1.015 (1.005 to 1.025)	
	insulin*BMI			0.972 (0.961 to 0.983)	
	Metformin*age			1.008 (1.004 to 1.012)	
	metformin*HBA1C			0.989 (0.986 to 0.992)	

	Other hypoglycaemic *BMI			1.030 (1.006 to 1.054)	
	sulphonylureas*HBA1C			0.967 (0.964 to 0.970)	
Amputation	glitazones[§]	0.80 (0.62 to 1.04)	0.73 (0.57 to 0.95)	0.76 (0.59 to 0.99)	0.78 (0.51 to 1.18)
	gliptins[§]	0.96 (0.78 to 1.18)	0.90 (0.73 to 1.10)	0.87 (0.71 to 1.07)	0.90 (0.67 to 1.22)
	metformin[§]	0.75 (0.68 to 0.81)	0.69 (0.63 to 0.76)	0.70 (0.63 to 0.76)	0.75 (0.67 to 0.84)
	sulphonylureas[§]	1.34 (1.22 to 1.47)	1.12 (1.01 to 1.23)	1.14 (1.03 to 1.27)	1.17 (1.01 to 1.37)
	insulin[§]	2.31 (1.99 to 2.68)	1.76 (1.51 to 2.04)	1.64 (1.41 to 1.91)	1.83 (1.41 to 2.38)
	Other hypoglycaemic [§]	1.02 (0.76 to 1.38)	0.91 (0.68 to 1.23)	0.91 (0.67 to 1.23)	0.74 (0.45 to 1.22)
	Sulphonylureas*age			0.985 (0.978 to 0.991)	
Kidney failure	glitazones[§]	0.91 (0.69 to 1.19)	0.74 (0.56 to 0.97)	1.05 (0.80 to 1.38)	0.84 (0.53 to 1.34)
	gliptins[§]	0.83 (0.65 to 1.07)	0.74 (0.57 to 0.95)	0.99 (0.77 to 1.27)	1.03 (0.73 to 1.46)
	metformin[§]	0.17 (0.16 to 0.19)	0.28 (0.25 to 0.31)	0.41 (0.37 to 0.46)	0.50 (0.44 to 0.57)
	sulphonylureas[§]	1.84 (1.68 to 2.01)	1.03 (0.94 to 1.13)	1.21 (1.10 to 1.33)	1.36 (1.17 to 1.58)
	insulin[§]	2.67 (2.33 to 3.07)	1.16 (1.01 to 1.34)	1.45 (1.25 to 1.68)	2.03 (1.60 to 2.57)
	Other hypoglycaemic [§]	1.18 (0.85 to 1.66)	0.83 (0.59 to 1.16)	0.80 (0.56 to 1.14)	0.91 (0.54 to 1.53)

Model A: adjusted for age, sex, ethnicity, deprivation, calendar year, duration of diabetes plus other diabetes drug classes

Model B: model A + comorbidities (hypertension; cardiovascular disease; atrial fibrillation; chronic renal disease; rheumatoid arthritis; valvular heart disease; peripheral vascular disease) + existing complications (history of hypoglycaemia; hyperglycaemia; amputation; severe kidney failure; blindness) + use of other drugs (statins, aspirin, anticoagulants, diuretics, ACE inhibitors/angiotensin blockers, beta blockers, calcium channel blockers)

Model C (Table 3 in main paper): model B + clinical values (body mass index, cholesterol/HDL ratio, systolic blood pressure, serum creatinine, glycosylated haemoglobin)

Model D: model C + significant interaction terms shown in the table

Model E: model C having excluded prevalent users of sulphonylureas

Web table 3 Adjusted hazard ratios with 95% confidence intervals for each outcome compared with no treatment. Treatment categories are mutually exclusive. Significantly increased hazard ratios are shown in red; decreased are shown in green. Non-significant results are shown in black.

	Blindness†	Hyperglycaemia †	Hypoglycaemia†	Amputation†	Kidney disease†
	Adjusted HR	Adjusted HR	Adjusted HR	Adjusted HR	Adjusted HR
No current treatment	1.00	1.00	1.00	1.00	1.00
Monotherapy					
Metformin alone±	0.71 (0.66 to 0.77)	0.63 (0.61 to 0.66)	0.33 (0.30 to 0.36)	0.70 (0.62 to 0.78)	0.54 (0.47 to 0.62)
Sulphonylureas alone±	1.01 (0.89 to 1.15)	0.88 (0.80 to 0.96)	2.39 (2.19 to 2.61)	1.00 (0.84 to 1.18)	1.42 (1.27 to 1.60)
Insulin alone±	1.39 (1.07 to 1.81)	1.57 (1.34 to 1.85)	6.93 (6.17 to 7.78)	1.86 (1.45 to 2.39)	1.56 (1.29 to 1.88)
Glitazones alone±	0.69 (0.22 to 2.16)	0.95 (0.49 to 1.83)	0.60 (0.19 to 1.86)	1.30 (0.42 to 4.06)	1.38 (0.62 to 3.10)
Gliptins alone±	0.99 (0.47 to 2.09)	0.91 (0.54 to 1.54)	0.27 (0.07 to 1.09)	0.71 (0.23 to 2.22)	1.91 (1.12 to 3.26)
Other hypoglycaemic drugs alone±	0.58 (0.19 to 1.81)	0.20 (0.05 to 0.82)	2.11 (1.19 to 3.72)	-	0.63 (0.34 to 1.17)
Dual therapy					
Metformin and sulphonylureas±	0.67 (0.61 to 0.74)	0.65 (0.60 to 0.69)	1.97 (1.84 to 2.11)	0.75 (0.66 to 0.85)	0.41 (0.34 to 0.49)
Metformin and insulin±	1.13 (0.86 to 1.48)	1.24 (1.03 to 1.49)	4.69 (4.12 to 5.35)	1.24 (0.93 to 1.64)	0.61 (0.35 to 1.06)
Metformin and glitazones±	0.62 (0.42 to 0.92)	0.38 (0.28 to 0.51)	0.44 (0.29 to 0.67)	0.40 (0.21 to 0.74)	0.38 (0.18 to 0.81)
Metformin and gliptins±	0.51 (0.35 to 0.74)	0.49 (0.39 to 0.61)	0.40 (0.28 to 0.59)	0.59 (0.38 to 0.90)	0.32 (0.15 to 0.67)
Metformin and other hypoglycaemic ±	0.59 (0.35 to 0.99)	0.67 (0.50 to 0.90)	0.91 (0.63 to 1.30)	0.65 (0.36 to 1.18)	0.31 (0.10 to 0.97)
Sulphonylureas and insulin±	1.52 (1.05 to 2.20)	1.66 (1.20 to 2.30)	7.83 (6.60 to 9.29)	1.49 (0.98 to 2.28)	1.93 (1.45 to 2.57)
Sulphonylureas and glitazones±	0.57 (0.27 to 1.20)	1.22 (0.77 to 1.95)	4.33 (3.31 to 5.65)	1.43 (0.79 to 2.61)	1.16 (0.69 to 1.94)
Sulphonylureas and gliptins±	0.94 (0.56 to 1.60)	0.62 (0.36 to 1.07)	1.94 (1.36 to 2.77)	0.91 (0.48 to 1.70)	1.74 (1.14 to 2.65)
Sulphonylureas and other hypoglycaemic ±	0.49 (0.12 to 1.97)	0.46 (0.15 to 1.44)	3.97 (2.49 to 6.32)	1.41 (0.52 to 3.77)	1.29 (0.61 to 2.74)
Triple therapy					
Metformin, sulphonylureas and insulin±	0.97 (0.69 to 1.35)	0.93 (0.71 to 1.21)	4.31 (3.69 to 5.03)	0.90 (0.61 to 1.32)	0.58 (0.29 to 1.16)
Metformin, sulphonylureas and glitazones±	0.48 (0.34 to 0.67)	0.63 (0.50 to 0.80)	2.07 (1.77 to 2.41)	0.49 (0.33 to 0.73)	0.66 (0.41 to 1.06)
Metformin, sulphonylureas and gliptins±	0.58 (0.44 to 0.77)	0.69 (0.57 to 0.84)	1.66 (1.42 to 1.94)	0.69 (0.51 to 0.92)	0.37 (0.21 to 0.65)
Metformin, sulphonylureas and other hypoglycaemic ±	0.65 (0.42 to 1.02)	0.65 (0.48 to 0.88)	1.41 (1.08 to 1.85)	0.59 (0.35 to 1.01)	0.51 (0.21 to 1.22)
All other drug combinations±	0.67 (0.45 to 0.99)	0.91 (0.72 to 1.14)	2.95 (2.48 to 3.51)	0.87 (0.60 to 1.27)	0.87 (0.53 to 1.41)

± compared with periods not on any treatment.

Notes: significantly increased HR shown in red; significantly decreased HR shown in green; non-significant results shown in black.

†Hazard ratios adjusted for the following: sex; age; calendar year; duration since diagnosis of diabetes (5 levels); ethnicity (9 levels) Townsend deprivation score, smoking status (5 levels); use of other diabetes drugs; use of anticoagulant thiazide ace angiotensin 2 blockers; calcium channel blockers; statins; aspirin; existing complications (blindness, hyperglycaemic coma; hypoglycaemia; amputation; severe kidney failure); hypertension; cardiovascular disease; atrial fibrillation; chronic renal disease; rheumatoid arthritis; valvular heart disease; peripheral vascular disease; body mass index; systolic blood pressure; HBA1C; serum creatinine; cholesterol/HDL ratio

Web table 4 Adjusted hazard ratios with 95% confidence intervals for each outcome compared with no current treatment, excluding prevalent users of sulphonylureas. Treatment categories are mutually exclusive.

	Blindness†	Hyperglycaemia †	Hypoglycaemia†	Amputation†	Kidney disease†
	Adjusted HR	Adjusted HR	Adjusted HR	Adjusted HR	Adjusted HR
No treatment	1.00	1.00	1.00	1.00	1.00
Monotherapy					
Metformin alone±	0.73 (0.67 to 0.79)	0.64 (0.62 to 0.67)	0.36 (0.33 to 0.40)	0.75 (0.66 to 0.85)	0.59 (0.51 to 0.68)
Sulphonylureas alone±	1.19 (0.97 to 1.47)	1.05 (0.91 to 1.21)	3.18 (2.76 to 3.68)	1.23 (0.93 to 1.64)	1.78 (1.47 to 2.15)
Insulin alone±	1.81 (1.28 to 2.56)	1.63 (1.36 to 1.96)	7.46 (6.39 to 8.72)	1.90 (1.28 to 2.83)	2.35 (1.75 to 3.15)
Glitazones alone±	0.80 (0.26 to 2.48)	0.93 (0.47 to 1.87)	0.89 (0.28 to 2.75)	1.72 (0.55 to 5.35)	0.96 (0.31 to 2.99)
Gliptins alone±	0.93 (0.39 to 2.24)	0.92 (0.52 to 1.63)	0.41 (0.10 to 1.64)	0.65 (0.16 to 2.63)	2.43 (1.33 to 4.43)
Other drugs alone±	0.71 (0.23 to 2.20)	0.23 (0.06 to 0.93)	2.47 (1.40 to 4.36)	n/a	1.43 (0.70 to 2.93)
Dual therapy					
Metformin & sulphonylureas±	0.71 (0.60 to 0.83)	0.80 (0.73 to 0.87)	2.46 (2.23 to 2.72)	0.88 (0.73 to 1.08)	0.52 (0.40 to 0.70)
Metformin & insulin±	0.93 (0.57 to 1.53)	1.04 (0.81 to 1.34)	5.98 (4.96 to 7.21)	1.64 (1.05 to 2.55)	1.03 (0.51 to 2.10)
Metformin and glitazones±	0.64 (0.42 to 0.98)	0.38 (0.28 to 0.52)	0.51 (0.32 to 0.80)	0.53 (0.28 to 1.00)	0.36 (0.16 to 0.82)
Metformin and gliptins±	0.53 (0.35 to 0.80)	0.50 (0.40 to 0.64)	0.44 (0.29 to 0.67)	0.66 (0.41 to 1.05)	0.40 (0.19 to 0.84)
Metformin and other hypoglycaemic ±	0.65 (0.38 to 1.10)	0.62 (0.45 to 0.85)	0.97 (0.65 to 1.43)	0.66 (0.33 to 1.33)	0.38 (0.12 to 1.20)
Sulphonylureas and insulin±	1.14 (0.43 to 3.05)	1.13 (0.61 to 2.11)	11.06 (8.09 to 15.11)	1.61 (0.60 to 4.32)	2.74 (1.61 to 4.65)
Sulphonylureas and glitazones±	n/a	1.09 (0.52 to 2.30)	7.17 (4.49 to 11.44)	1.98 (0.64 to 6.17)	1.40 (0.52 to 3.80)
Sulphonylureas and gliptins±	1.06 (0.47 to 2.37)	0.56 (0.26 to 1.17)	2.30 (1.30 to 4.06)	1.39 (0.58 to 3.38)	1.79 (0.88 to 3.62)
Sulphonylureas and other hypoglycaemic ±	1.35 (0.19 to 9.58)	0.79 (0.20 to 3.18)	6.03 (2.70 to 13.48)	1.77 (0.25 to 12.64)	n/a
Triple therapy					
Metformin, sulphonylureas and insulin±	1.16 (0.55 to 2.44)	1.02 (0.67 to 1.56)	7.10 (5.37 to 9.40)	1.04 (0.43 to 2.51)	0.88 (0.22 to 3.55)
Metformin, sulphonylureas and glitazones±	0.84 (0.46 to 1.52)	0.72 (0.51 to 1.02)	3.15 (2.36 to 4.20)	0.47 (0.17 to 1.25)	0.87 (0.36 to 2.13)
Metformin, sulphonylureas and gliptins±	0.51 (0.30 to 0.86)	0.59 (0.45 to 0.78)	2.55 (2.03 to 3.21)	0.96 (0.61 to 1.53)	0.26 (0.08 to 0.80)
Metformin, sulphonylureas and other hypoglycaemic ±	0.52 (0.17 to 1.61)	0.69 (0.42 to 1.13)	1.58 (0.91 to 2.74)	0.41 (0.10 to 1.63)	0.41 (0.06 to 2.92)
All other drug combinations±	0.71 (0.38 to 1.33)	1.04 (0.78 to 1.37)	3.54 (2.74 to 4.57)	0.65 (0.31 to 1.37)	0.96 (0.45 to 2.04)

± compared with periods not on any treatment.

Notes: significantly increased HR shown in red; significantly decreased HR shown in green; non-significant results shown in black.
†Hazard ratios adjusted for the following: sex; age; duration since diagnosis of diabetes (5 levels); ethnicity (9 levels) Townsend deprivation score smoking status (5 levels) use of anticoagulant thiazide ace angiotensin 2 blockers; calcium channel blockers; statins; aspirin; existing complications (blindness, hyperglycaemic coma; hypoglycaemia; amputation; severe kidney failure); hypertension; cardiovascular disease; atrial fibrillation; chronic renal disease; rheumatoid arthritis; valvular heart disease; peripheral vascular disease; body mass index; systolic blood pressure; HBA1C; serum creatinine; cholesterol/HDL ratio