

SUPPLEMENTARY DATA

Supplementary Table 1. Characteristics of patients experiencing at least one any or major hypoglycemic event, by treatment allocation, by updated HbA1c and medication list

		Any hypoglycemia				Major hypoglycemia			
		Saxagliptin	Placebo	HR	P ⁺	Saxagliptin	Placebo	HR	P ⁺
Updated HbA1c	<6.5	120 / 1292 (9.3%)	84 / 941 (8.9%)	1.04 (0.79, 1.38)	0.557	18 / 1375 (1.3%)	12 / 968 (1.2%)	1.05 (0.51, 2.24)	0.480
	≥6.5-7	261 / 1487 (17.6%)	164 / 1254 (13.1%)	1.36 (1.12, 1.66)		33 / 1489 (2.2%)	18 / 1266 (1.4%)	1.47 (0.84, 2.67)	
	≥7-8	499 / 2520 (19.8%)	439 / 2574 (17.1%)	1.19 (1.05, 1.36)		64 / 2507 (2.6%)	41 / 2565 (1.6%)	1.62 (1.10, 2.41)	
	≥8-9	316 / 1507 (21.0%)	304 / 1603 (19.0%)	1.15 (0.98, 1.35)		29 / 1481 (2.0%)	34 / 1610 (2.1%)	0.96 (0.58, 1.57)	
	≥9	259 / 1455 (17.8%)	283 / 1825 (15.5%)	1.17 (0.99, 1.39)		32 / 1414 (2.3%)	35 / 1791 (2.0%)	1.17 (0.72, 1.89)	
	≤7	445 / 3085 (14.4%)	292 / 2489 (11.7%)	1.25 (1.08-1.45)	0.432	63 / 3156 (2.0%)	32 / 2536 (1.3%)	1.57 (1.03-2.43)	0.242
	>7	1010 / 5176 (19.5%)	982 / 5708 (17.2%)	1.17 (1.07-1.28)		113 / 5110 (2.2%)	108 / 5664 (1.9%)	1.18 (0.90-1.53)	
Updated medication and updated HbA1c	No antidiabetic medications	17 / 352 (4.8%)	12 / 334 (3.6%)	1.42 (0.68, 3.06)	0.003	5 / 367 (1.4%)	2 / 343 (0.6%)	2.57 (0.55, 18.06)	0.598
	Metformin alone or with other OHA's excluding SUR or glinides	76 / 1586 (4.8%)	56 / 1483 (3.8%)	1.27 (0.90, 1.80)		5 / 1605 (0.3%)	2 / 1495 (0.1%)	2.39 (0.51, 16.69)	
	SUR alone or with other OHA's	394 / 2559 (15.4%)	245 / 2434 (10.1%)	1.59 (1.36, 1.87)		41 / 2515 (1.6%)	23 / 2407 (1.0%)	1.73 (1.05, 2.93)	
	Long acting insulin without SUR and without short or intermediate acting insulin	63 / 358 (17.6%)	60 / 389 (15.4%)	1.19 (0.84, 1.70)		9 / 373 (2.4%)	9 / 395 (2.3%)	1.11 (0.43, 2.84)	
	Long acting insulin with SUR and without short or intermediate acting insulin	55 / 296 (18.6%)	66 / 355 (18.6%)	1.01 (0.71, 1.45)		4 / 292 (1.4%)	3 / 349 (0.9%)	1.48 (0.33, 7.52)	
	Intermediate acting insulin (without short or long acting insulin)	101 / 408 (24.8%)	115 / 468 (24.6%)	1.02 (0.78, 1.33)		16 / 405 (4.0%)	11 / 464 (2.4%)	1.72 (0.80, 3.80)	
	Other insulin regimen including short acting insulin	740 / 2588 (28.6%)	714 / 2610 (27.4%)	1.07 (0.97, 1.19)		96 / 2593 (3.7%)	90 / 2620 (3.4%)	1.07 (0.81, 1.43)	
	Other antidiabetic medications	16/133 (12.0%)	9/139 (6.5%)	1.91 (0.86, 4.52)		1/130 (0.8%)	0/139 (0.0%)	NA	
	Taking SUR	568 / 3329 (17.1%)	422 / 3313 (12.7%)	1.38 (1.22, 1.57)	0.665	58 / 3272 (1.8%)	37 / 3269 (1.1%)	1.58 (1.05, 2.41)	0.366
	HbA1c ≤7	208 / 1125 (18.5%)	123 / 927 (13.3%)	1.43 (1.14-1.79)		30 / 1128 (2.7%)	13 / 917 (1.4%)	1.82 (0.97-3.62)	
	HbA1c >7	355 / 2194 (16.2%)	297 / 2382 (12.5%)	1.35 (1.16-1.58)		27 / 2137 (1.3%)	24 / 2350 (1.0%)	1.27 (0.73-2.21)	
	Not taking SUR	894 / 4951 (18.1%)	855 / 4899 (17.5%)	1.05 (0.96, 1.15)		119 / 5008 (2.4%)	103 / 4943 (2.1%)	1.15 (0.89, 1.51)	

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	HbA1c ≤7	237 / 1960 (12.1%)	169 / 1562 (10.8%)	1.13 (0.93-1.38)	0.743	33 / 2028 (1.6%)	19 / 1619 (1.2%)	1.41 (0.81-2.53)	0.544
	HbA1c >7	655 / 2982 (22.0%)	685 / 3326 (20.6%)	1.09 (0.98-1.21)		86 / 2973 (2.9%)	84 / 3314 (2.5%)	1.16 (0.85-1.56)	
	Taking insulin	959 / 3650 (26.3%)	955 / 3822 (25.0%)	1.08 (0.98, 1.18)		125 / 3663 (3.4%)	113 / 3828 (3.0%)	1.15 (0.90, 1.49)	
	HbA1c ≤7	222 / 824 (26.9%)	153 / 661 (23.1%)	1.20 (0.98-1.48)	0.264	32 / 853 (3.8%)	20 / 707 (2.8%)	1.33 (0.77-2.37)	0.546
	HbA1c >7	734 / 2819 (26.0%)	800 / 3156 (25.3%)	1.05 (0.95-1.16)		93 / 2806 (3.3%)	93 / 3118 (3.0%)	1.11 (0.84-1.49)	
Type of SUR ^{*+}	Glibenclamide	197/1,096 (18.0%)	131/1,074 (12.2%)	1.55 (1.24-1.93)	0.519	31/1,066 (2.9%)	18/1,053 (1.7%)	1.73 (0.98-3.16)	0.938
	Glimepiride	160/1,000 (16.0%)	126/1,002 (12.6%)	1.28 (1.01-1.62)		13/982 (1.3%)	9/988 (0.9%)	1.32 (0.56-3.24)	
	Glipizide	82/434 (18.9%)	73/460 (15.9%)	1.23 (0.90-1.69)		8/429 (1.9%)	5/451 (1.1%)	1.65 (0.55-5.47)	
	Gliclazide	114/705 (16.2%)	77/695 (11.1%)	1.52 (1.14-2.03)		6/703 (0.9%)	5/697 (0.7%)	1.16 (0.35-4.04)	

Table legend: +P values represent interaction between subgroups and treatment allocation. *The interaction p-value for updated medications does not contain the category “Other medications” SUR – sulfonylurea; OHA – oral hypoglycemia agents. *+Amongst patients taking SUR – excluding those taking more than one type of SUR, excluding tolbutamide and other SUR use.

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Supplementary Table 2. Adjusted association of patient's variables with risk for "any" or "major" hypoglycemia – using updated HbA1c and medications list

		N	N (%) with hypoglycemia	Adjusted model HR	p	N	N (%) with major hypoglycemia	Adjusted model HR	p
Overall		16492	2739 (16.6%)			16492	317 (1.9%)		
Age	<65	7931	1231 (15.5%)	1		7931	109 (1.4%)	1	
	≥65-≤75	6650	1184 (17.8%)	1.07 (0.98, 1.16)	0.120	6650	146 (2.2%)	1.30 (1.00,1.69)	0.055
	>75	1911	324 (17.0%)	1.03 (0.90, 1.17)	0.683	1911	62 (3.2%)	1.83 (1.29,2.58)	<.001
Sex	Female	5455	903 (16.6%)	1		5455	111 (2.0%)	1	
	Male	11037	1836 (16.6%)	1.04 (0.96, 1.13)	0.309	11037	206 (1.9%)	1.05 (0.83,1.34)	0.676
Race	White	12407	2113 (17.0%)	1		12047	234 (1.9%)	1	
	Black or African American	568	109 (19.2%)	1.17 (0.96, 1.42)	0.110	568	20 (3.5%)	1.87 (1.11,2.95)	0.011
	Asian	1780	293 (16.5%)	1.02 (0.89, 1.16)	0.786	1780	28 (1.6%)	0.86 (0.56,1.29)	0.494
	Other**	1737	224 (12.9%)	0.84 (0.72, 0.97)	0.021	1737	35 (2.0%)	1.24 (0.83,1.80)	0.275
BMI	≤30	7650	1231 (16.1%)	1		7650	160 (2.1%)	1	
	>30	8813	1503 (17.1%)	0.93 (0.86, 1.01)	0.094	8813	157 (1.8%)	0.74 (0.59,0.94)	0.015
Duration of diabetes	<5	3916	309 (7.9%)	1		3916	22 (0.6%)	1	
	≥5-10	3925	497 (12.7%)	1.23 (1.06,1.42)	0.006	3925	57 (1.5%)	1.86 (1.14,3.14)	0.015
	≥10-15	3500	623 (17.8%)	1.45 (1.25,1.67)	<.001	3500	66 (1.9%)	1.78 (1.10,3.00)	0.023
	≥15-20	2111	517 (24.5%)	1.86 (1.60,2.16)	<.001	2111	57 (2.7%)	2.09 (1.26,3.57)	0.005
	≥20	3025	792 (26.2%)	1.87 (1.62,2.17)	<.001	3025	115 (3.8%)	2.56 (1.60,4.26)	<.001
Updated HbA1c	<6.5	2233	204 (9.1%)	1		2343	30 (1.3%)	1	
	≥6.5-7	2741	425 (15.5%)	1.54 (1.31, 1.83)	<0.001	2755	51 (1.9%)	1.24 (0.79, 1.99)	0.354
	≥7-8	5094	938 (18.4%)	1.44 (1.23, 1.69)	<0.001	5072	105 (2.1%)	1.16 (0.77, 1.79)	0.498
	≥8-9	3110	620 (19.9%)	1.36 (1.15, 1.61)	<0.001	3091	63 (2.0%)	0.97 (0.62, 1.55)	0.908
	≥9	3280	542 (16.5%)	1.11 (0.94, 1.32)	0.222	3205	67 (2.1%)	1.05 (0.67, 1.67)	0.846
ACR	<30	9696	1544 (15.9%)	1		9696	136 (1.4%)	1	
	≥30-300	4426	782 (17.7%)	0.92 (0.84,1.00)	0.061	4426	115 (2.6%)	1.39 (1.08,1.80)	0.010
	≥300	1638	316 (19.3%)	0.85 (0.75,0.97)	0.014	1638	53 (3.2%)	1.22 (0.86,1.72)	0.250
RF*	Normal-mild	13916	2177 (15.6%)	1		13916	199 (1.4%)	1	
	Moderate	2240	487 (21.7%)	1.18 (1.06,1.31)	0.003	2240	98 (4.4%)	2.09 (1.60,2.72)	<.001
	severe	336	75 (22.3%)	1.08 (0.84,1.37)	0.536	336	20 (6.0%)	2.29 (1.35,3.70)	0.001

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No antidiabetic medications		686	29 (4.2%)	1		710	7 (1.0%)	1	
Metformin alone or with other OHA besides SUR or glinides		3069	132 (4.3%)	0.91 (0.61, 1.38)	0.633	3100	7 (0.2%)	0.25 (0.08, 0.73)	0.009
SUR alone or with other OHA		4993	639 (12.8%)	2.51 (1.75, 3.73)	<0.001	4922	64 (1.3%)	1.05 (0.51, 2.56)	0.896
Long acting insulin without SUR and without short or intermediate acting insulin		747	123 (16.5%)	3.04 (2.05, 4.68)	<0.001	768	18 (2.3%)	1.74 (0.74, 4.56)	0.223
Long acting insulin with SUR and without short or intermediate acting insulin		651	121 (18.6%)	3.51 (2.36, 5.41)	<0.001	641	7 (1.1%)	0.88 (0.30, 2.62)	0.820
Intermediate acting insulin (without short or long acting insulin)		876	216 (24.7%)	5.01 (3.43, 7.60)	<0.001	869	27 (3.1%)	2.14 (0.95, 5.48)	0.083
Other insulin regimen including short acting insulin		5198	1454 (28.0%)	5.41 (3.79, 8.05)	<0.001	5213	186 (3.6%)	2.52 (1.24, 6.06)	0.021
Other medications		272	25 (9.2%)	1.80 (1.03, 3.09)	0.035	269	1 (0.4%)	0.28 (0.02, 1.61)	0.240
Treatment arm	Placebo	8212	1277 (15.6%)	1	1	8212	140 (1.7%)	1	1
	Saxagliptin	8280	1462 (17.7%)	1.17 (1.08, 1.26)	<0.001	8280	177 (2.1%)	1.26 (1.01, 1.58)	0.045

Table legend: * Renal function categories defined as Normal function – Mild impairment (eGFR >50 mL/min), Moderate impairment (eGFR 30 to 50 mL/min), and Severe impairment (eGFR <30 mL/min). ** Other – Multiracial, Native Hawaiian, other Pacific, American Indian or Alaska native. RF – renal failure; ACR – albumin creatinine ratio; SUR – sulfonylurea; OHA – oral hypoglycemia agent

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Supplementary Table 3. Adjusted association of baseline variables with risk for any or major hypoglycemia

		N	N (%) with hypoglycemia	Adjusted model HR	p	N (%) with major hypoglycemia	Adjusted model HR	p
Overall		16492	2739 (16.6%)			317 (1.9%)		
Age	<65	7931	1231 (15.5%)	1		109 (1.4%)	1	
	≥65-≤75	6650	1184 (17.8%)	1.08 (0.99, 1.17)	0.082	146 (2.2%)	1.30 (1.00,1.70)	0.051
	>75	1911	324 (17.0%)	1.03 (0.90, 1.17)	0.671	62 (3.2%)	1.84 (1.30,2.59)	<.001
Sex	Female	5455	903 (16.6%)	1		111 (2.0%)	1	
	Male	11037	1836 (16.6%)	1.04 (0.96, 1.13)	0.364	206 (1.9%)	1.04 (0.82,1.33)	0.745
Race	White	12407	2113 (17.0%)	1		234 (1.9%)	1	
	Black or African American	568	109 (19.2%)	1.16 (0.95, 1.40)	0.142	20 (3.5%)	1.85 (1.10,2.91)	0.013
	Asian	1780	293 (16.5%)	1.04 (0.91, 1.18)	0.586	28 (1.6%)	0.89 (0.57,1.33)	0.592
	Other**	1737	224 (12.9%)	0.86 (0.74, 1.00)	0.052	35 (2.0%)	1.27 (0.85,1.85)	0.222
BMI	≤30	7650	1231 (16.1%)	1		160 (2.1%)	1	
	>30	8813	1503 (17.1%)	0.92 (0.85, 1.00)	0.049	157 (1.8%)	0.73 (0.58,0.93)	0.011
Duration of diabetes	<5	3916	309 (7.9%)	1		22 (0.6%)	1	
	≥5-10	3925	497 (12.7%)	1.24 (1.07,1.44)	0.004	57 (1.5%)	1.85 (1.14,3.13)	0.016
	≥10-15	3500	623 (17.8%)	1.44 (1.24,1.67)	<.001	66 (1.9%)	1.74 (1.07,2.93)	0.031

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	≥15-20	2111	517 (24.5%)	1.80 (1.54,2.10)	<.001	57 (2.7%)	2.03 (1.22,3.49)	0.008
	≥20	3025	792 (26.2%)	1.83 (1.58,2.13)	<.001	115 (3.8%)	2.50 (1.56,4.18)	<.001
Baseline HbA1c	<6.5	1263	139 (11.0%)	1		19 (1.5%)	1	
	≥6.5-7	2856	391 (13.7%)	1.07 (0.88,1.31)	0.492	48 (1.7%)	0.98 (0.58,1.73)	0.936
	≥7-8	5416	947 (17.5%)	1.03 (0.86,1.24)	0.763	109 (2.0%)	0.82 (0.50,1.41)	0.440
	≥8-9	3139	651 (20.7%)	1.01 (0.84,1.23)	0.885	62 (2.0%)	0.68 (0.40,1.20)	0.162
	≥9	3525	576 (16.3%)	0.79 (0.65,0.97)	0.019	76 (2.2%)	0.76 (0.45,1.33)	0.311
ACR	<30	9696	1544 (15.9%)	1		136 (1.4%)	1	
	≥30-300	4426	782 (17.7%)	0.93 (0.85,1.02)	0.130	115 (2.6%)	1.42 (1.10,1.83)	0.007
	≥300	1638	316 (19.3%)	0.87 (0.77,0.99)	0.041	53 (3.2%)	1.28 (0.90,1.80)	0.158
RF*	Nor-mild	13916	2177 (15.6%)	1		199 (1.4%)	1	
	Moderate	2240	487 (21.7%)	1.17 (1.05,1.30)	0.004	98 (4.4%)	2.11 (1.61,2.75)	<.001
	severe	336	75 (22.3%)	1.07 (0.83,1.35)	0.592	20 (6.0%)	2.34 (1.38,3.77)	<.001
Beta blockers at baseline	No	6328	955 (15.1%)	1		115 (1.8%)	1	
	Yes	10162	1784 (17.6%)	1.03 (0.95,1.12)	0.453	202 (2.0%)	1.00 (0.78,1.27)	0.976
ACE Inhibitors at baseline	No	7550	1221 (16.2%)	1		138 (1.8%)	1	
	Yes	8940	1518 (17.0%)	1.03 (0.95,1.11)	0.501	179 (2.0%)	1.12 (0.89,1.41)	0.353

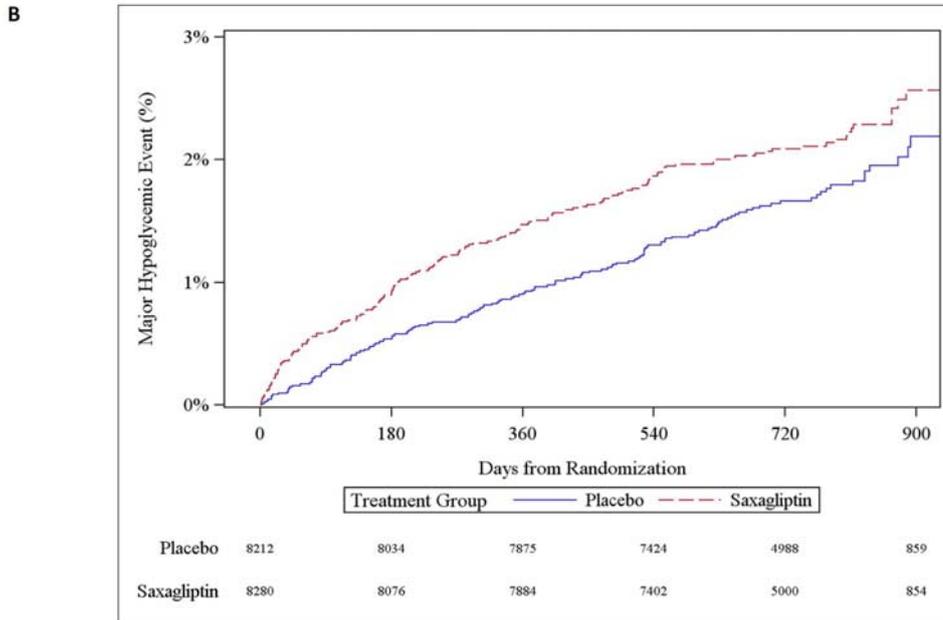
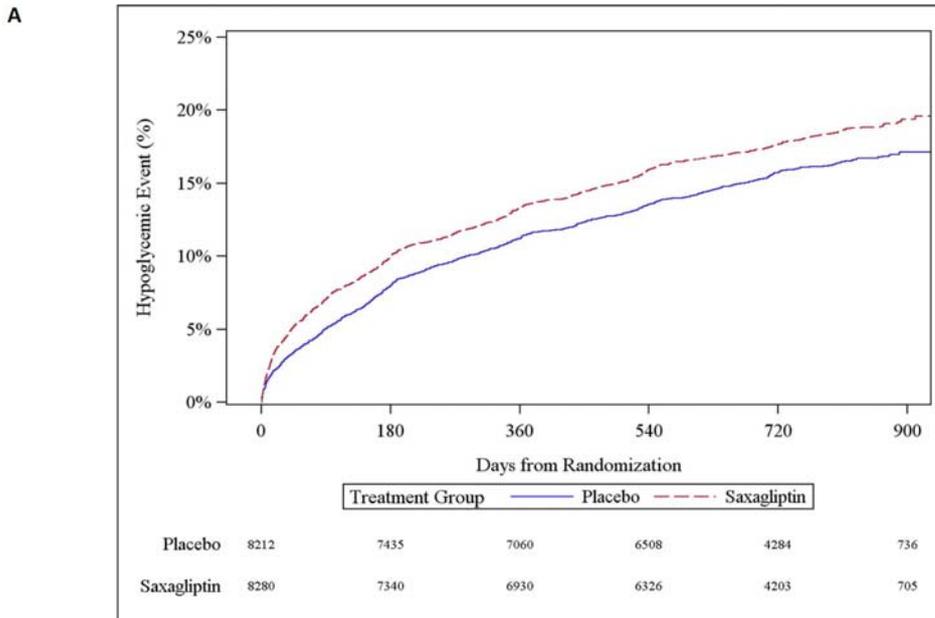
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No baseline antidiabetic medications		787	38 (4.8%)	1		4 (0.5%)	1	
Metformin alone or with other OHA besides SUR or glinides		3402	180 (5.3%)	1.00 (0.71,1.44)	0.984	13 (0.4%)	0.76 (0.27,2.72)	0.637
SUR alone or with other OHA		5226	662 (12.7%)	2.21 (1.61,3.13)	<.001	73 (1.4%)	2.06 (0.84,6.83)	0.165
Long acting insulin without SUR and without short or intermediate acting insulin		655	125 (19.1%)	3.30 (2.30,4.85)	<.001	16 (2.4%)	3.52 (1.27,12.46)	0.027
Long acting insulin with SUR and without short or intermediate acting insulin		531	114 (21.5%)	3.63 (2.51,5.36)	<.001	9 (1.7%)	2.32 (0.72,8.84)	0.176
Intermediate acting insulin (without short or long acting insulin)		815	195 (23.9%)	4.34 (3.07,6.30)	<.001	21 (2.6%)	3.48 (1.29,12.16)	0.025
Other insulin regimen including short acting insulin		4786	1400 (29.3%)	5.28 (3.84,7.48)	<.001	179 (3.7%)	5.19 (2.12,17.19)	0.002
Other medications		288	25 (8.7%)	1.40 (0.82,2.33)	0.209	2 (0.7%)	0.92 (0.13,4.77)	0.926
Treatment arm	Placebo	8212	1277 (15.6%)	1		140 (1.7%)	1	
	Saxagliptin	8280	1462 (17.7%)	1.14 (1.06,1.23)	<.001	177 (2.1%)	1.24 (0.99,1.56)	0.061

Table legend: The data is based on a multivariable Cox model adjusted for all covariates listed in this table * Renal function categories defined as Normal function – Mild impairment (eGFR >50 mL/min), Moderate impairment (eGFR 30 to 50 mL/min), and Severe impairment (eGFR <30 mL/min). ** Other – Multiracial, Native Hawaiian, other Pacific, American Indian or Alaska native. RF – renal failure; ACR – albumin creatinine ratio; SUR – sulfonylureas; OHA – oral hypoglycemic agents

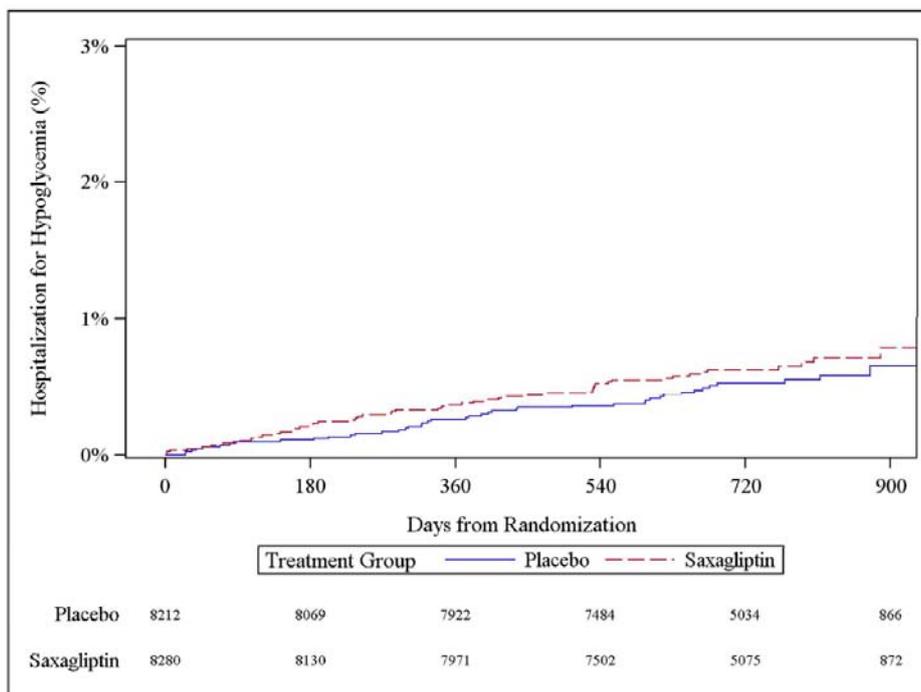
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Supplementary Figure 1. KM curves of time to (A) any hypoglycemia, (B) major hypoglycemia and (C) hospitalization for hypoglycemia



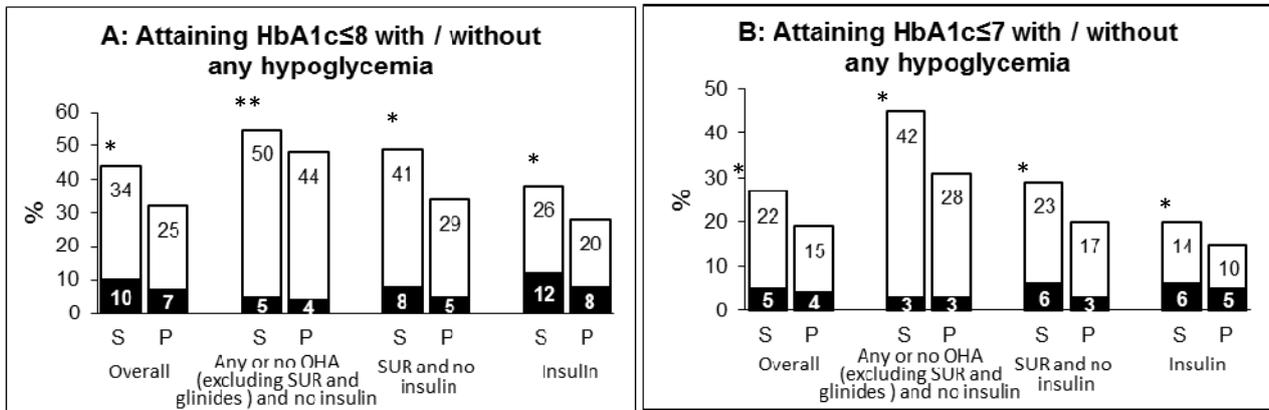
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Supplementary Figure 2. The proportions of attaining glycemic targets with / without hypoglycemia with saxagliptin vs. placebo under different baseline treatments



Legend: Proportions of achieving glycemic targets with (black bars) / without (white bars) hypoglycemia with saxagliptin or placebo by baseline medications. A: Amongst patients with baseline HbA1c >8.0% (>64 mmol/mol) and established CV disease, the proportions of patients with HbA1c to ≤8.0% (≤64mmol/mol) by the end of the trial with / without any hypoglycemic events. B: Amongst patients with baseline HbA1c >7.0% (≥53 mmol/mol) the proportions of patients with HbA1c to ≤7.0% (<53mmol/mol) by the end of the trial with / without any hypoglycemic events. S – Saxagliptin; P – Placebo; OHA – Oral hypoglycemic agents SUR – sulfonylurea. * p<0.0001 for attaining glycemic target overall between saxagliptin vs. placebo. ** p=0.075 for attaining glycemic target overall between saxagliptin vs. placebo.