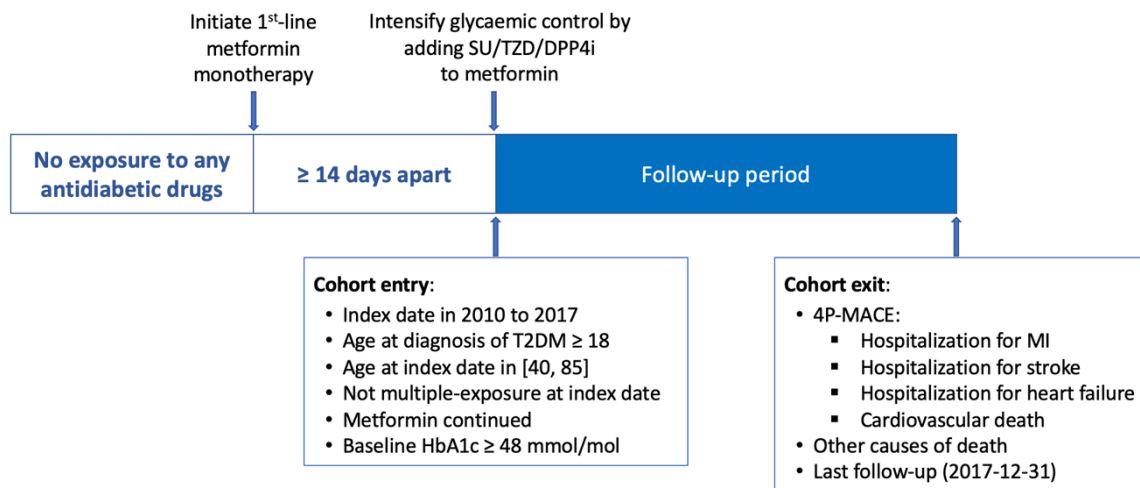


Supplementary Materials

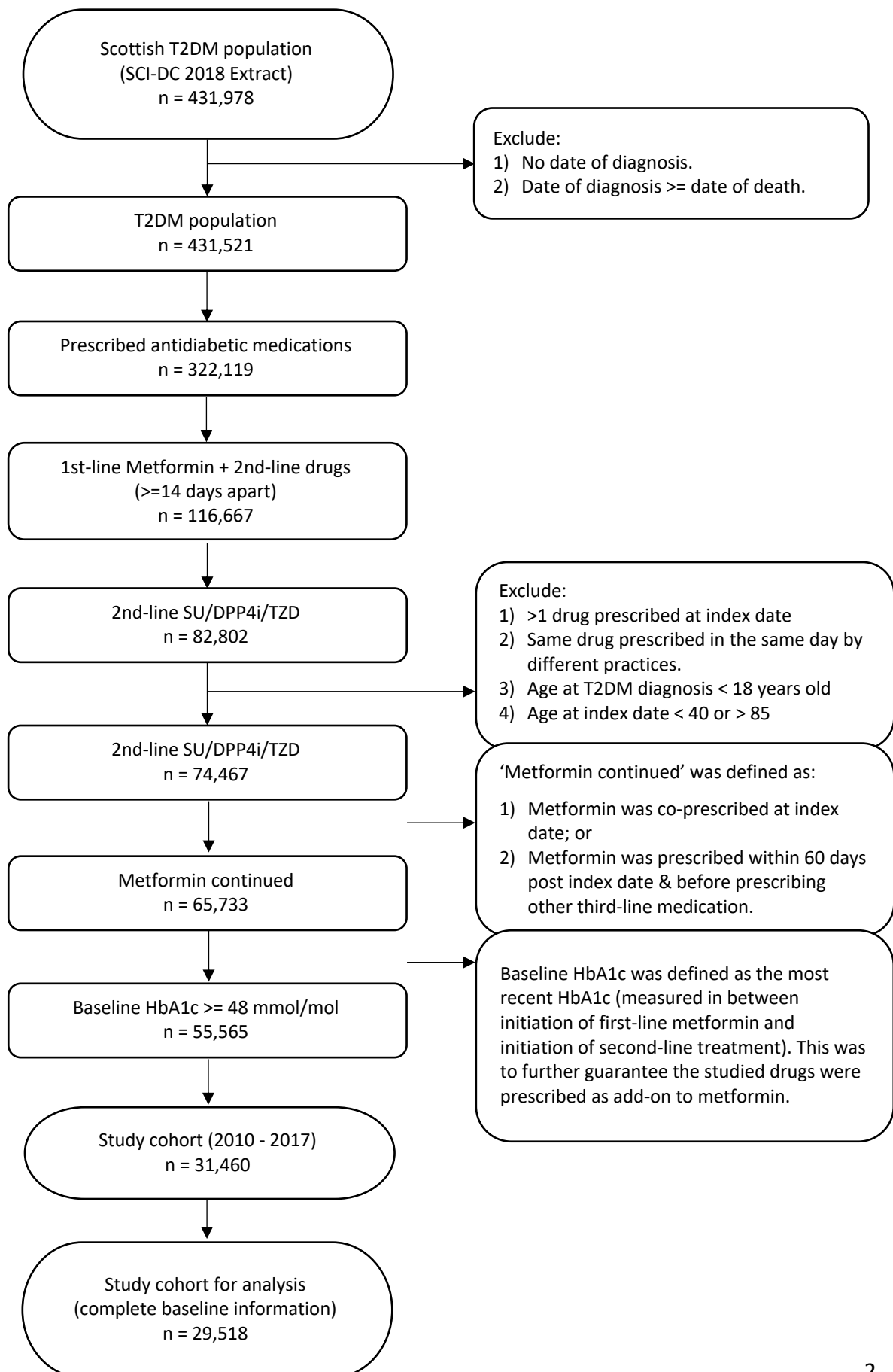
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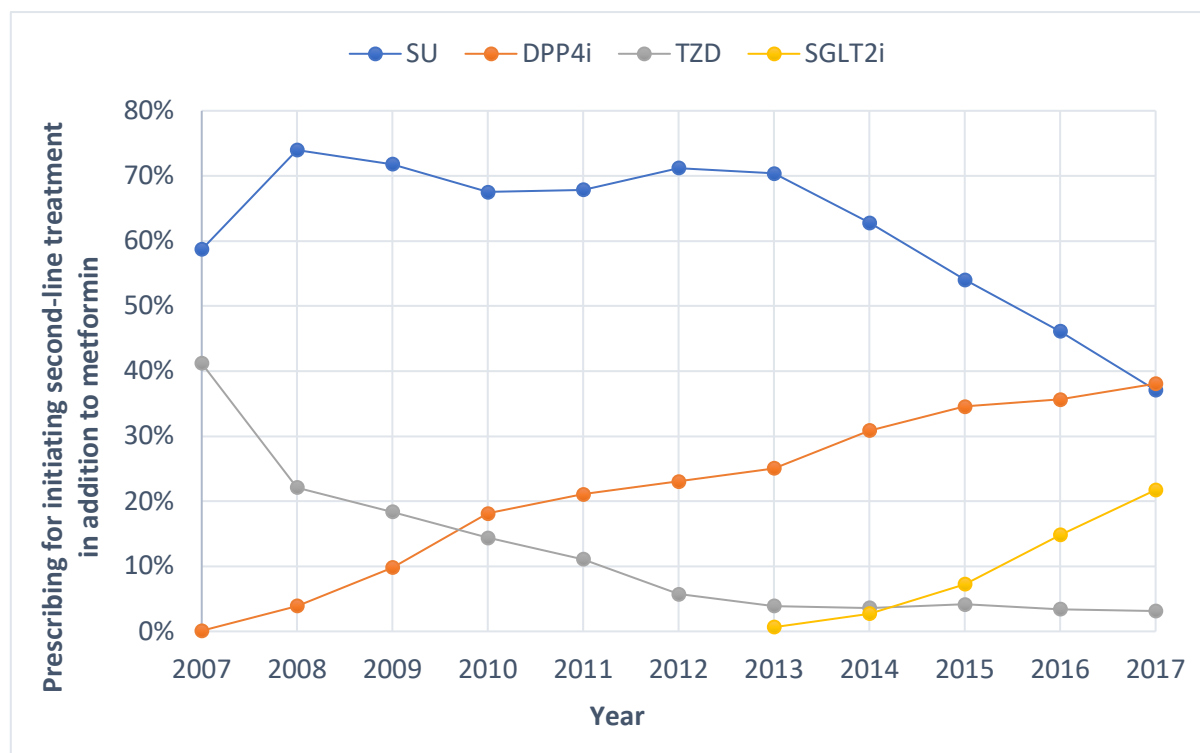
sFigure 1. Illustration of study design



sFigure 2. Flowchart showing attrition of patients and identification of the study cohort.

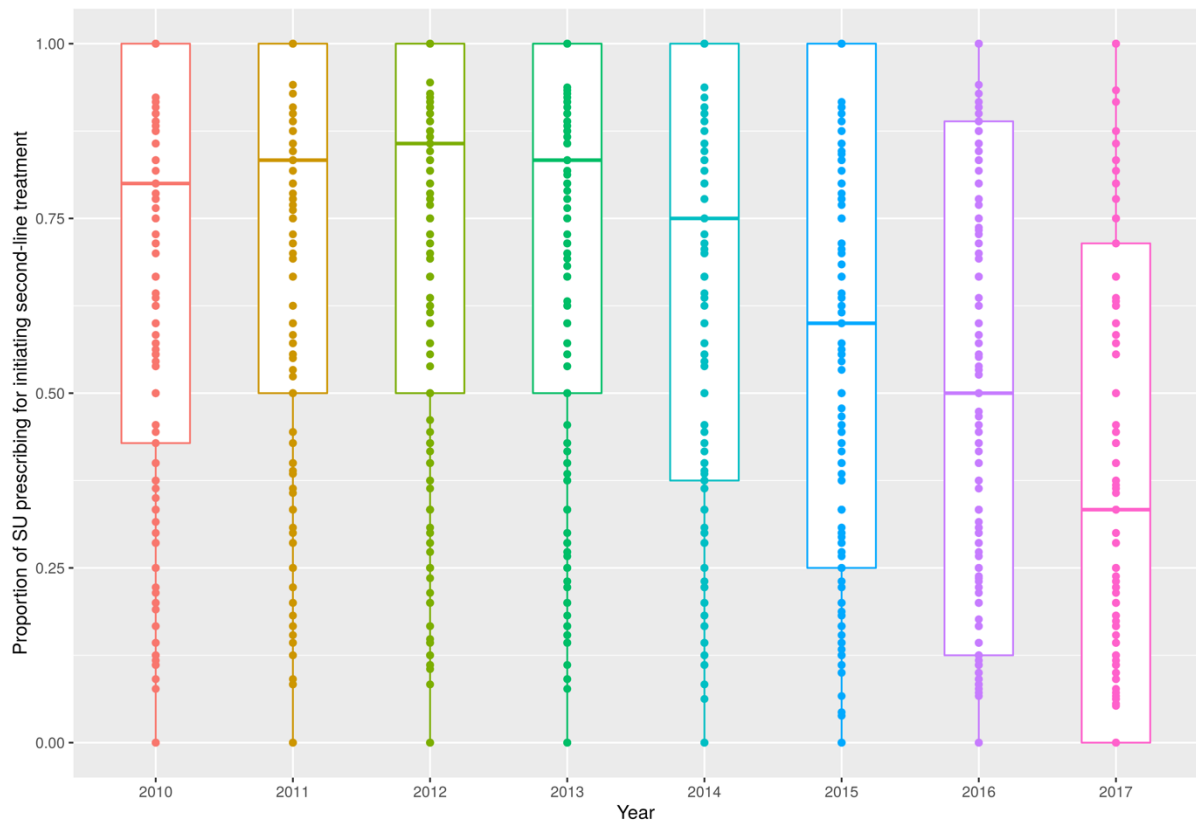


sFigure 3. Temporal trends of prescribing for second-line treatment in addition to metformin for people with type 2 diabetes in Scotland between 2007 and 2017.



The patterns of prescribing for initiating treatment intensification varied substantially. Between 2010 and 2013, SU accounted for around 70% of all the second-line treatment initiations. This percentage declined dramatically after 2013, and in 2017 SU accounted for 37% of the second-line treatment initiations, slightly less than DPP4i (38%). Prescribing for TZD remained low during the study period with a declining trend from 14% in 2010 to only 3% in 2017. Prescribing for SGLT2i started from 2013 in Scotland and has increased rapidly after guideline recommendation in 2015. In 2017, SGLT2i accounted for nearly 22% of the second-line initiated drugs. However, due to the low absolute number of prescriptions, insufficient follow-up time, and established cardio-protective effects, SGLT2i were not included as one of the comparators in further analyses.

sFigure 4. Boxplots of practice-level proportion of SU prescribing for initiating second-line treatment in addition to metformin among people with type 2 diabetes in Scotland between 2010 and 2017.



Between-practice variation of SU prescribing for initiating second-line treatment was found to be substantial. Within each year between 2007 to 2017, some practices only prescribed SU, while some others hardly ever prescribed SU. This suggests that the practice-level proportion of SU prescriptions is a good instrument for our IV analyses.

sTable 1. Incidence rates of study outcomes among people with type 2 diabetes in Scotland treated with sulphonylureas (SU), DPP-4 inhibitors (DPP4i) or thiazolidinediones (TZD) as second-line treatment in addition to metformin between 2010 and 2017.

	No. patients	No. events	Person years	Median (IQR) follow-up years	Incidence rate (95% CI) per 1000 person years
<u>4P-MACE</u>					
SU	18531	1709	72958.6	3.9 (2.1 to 5.7)	23.4 (22.3 to 24.6)
Non-SU	10987	701	37567.8	3.0 (1.5 to 5.2)	18.7 (17.3 to 20.1)
DPP4i	9114	541	28611.9	2.8 (1.3 to 4.7)	18.9 (17.3 to 20.6)
TZD	1873	160	8955.8	5.3 (2.7 to 6.9)	17.9 (15.2 to 20.9)
<u>Hospitalization for MI</u>					
SU	18531	528	74233.3	4.0 (2.2 to 5.7)	7.1 (6.5 to 7.7)
Non-SU	10987	211	38063.2	3.1 (1.6 to 5.3)	5.5 (4.8 to 6.3)
DPP4i	9114	169	28965.8	2.8 (1.4 to 4.8)	5.8 (5.0 to 6.8)
TZD	1873	42	9097.4	5.5 (2.8 to 6.9)	4.6 (3.3 to 6.2)
<u>Hospitalization for stroke</u>					
SU	18531	379	74653.0	4.1 (2.2 to 5.8)	5.1 (4.6 to 5.6)
Non-SU	10987	183	38132.2	3.1 (1.6 to 5.3)	4.8 (4.1 to 5.5)
DPP4i	9114	144	29011.5	2.8 (1.4 to 4.8)	5.0 (4.2 to 5.8)
TZD	1873	39	9120.7	5.5 (2.8 to 6.9)	4.3 (3.0 to 5.8)
<u>Hospitalization for HF</u>					
SU	18531	257	74555.1	4.1 (2.2 to 5.8)	3.4 (3.0 to 3.9)
Non-SU	10987	79	38207.5	3.1 (1.6 to 5.4)	2.1 (1.6 to 2.6)
DPP4i	9114	54	29112.6	2.8 (1.4 to 4.8)	1.9 (1.4 to 2.4)
TZD	1873	25	9094.9	5.5 (2.8 to 6.9)	2.7 (1.8 to 4.1)
<u>Cardiovascular death</u>					
SU	18531	916	75346.1	4.1 (2.3 to 5.8)	12.2 (11.4 to 13.0)
Non-SU	10987	355	38462.5	3.1 (1.6 to 5.4)	9.2 (8.3 to 10.2)
DPP4i	9114	269	29268.8	2.8 (1.4 to 4.8)	9.2 (8.1 to 10.4)
TZD	1873	86	9193.7	5.6 (2.9 to 6.9)	9.4 (7.5 to 11.6)
<u>All-cause death</u>					
SU	18531	1601	75346.1	4.1 (2.3 to 5.8)	21.2 (20.2 to 22.3)
Non-SU	10987	618	38462.5	3.1 (1.6 to 5.4)	16.1 (14.8 to 17.4)
DPP4i	9114	469	29268.8	2.8 (1.4 to 4.8)	16.0 (14.6 to 17.5)
TZD	1873	149	9193.7	5.6 (2.9 to 6.9)	16.2 (13.7 to 19.0)

sMethod 1. Subgroup analyses

sTable 2. Comparison of outcome rates between sulphonylureas (SU) and non-SU agents (DPP4i or TZD) in subgroups of cohort stratified by prior history of MACE, age, BMI, and subtypes of SU.

	4P-MACE	Hospitalization for MI	Hospitalization for stroke	Hospitalization for heart failure	Cardiovascular death	All-cause death
MACE history						
No prior MACE (n = 25,943)	1.05 (0.94 to 1.17)	1.19 (0.98 to 1.44)	0.89 (0.72 to 1.10)	1.37 (0.97 to 1.93)	1.05 (0.90 to 1.24)	1.05 (0.94 to 1.18)
Prior MACE (n = 3,575)	0.89 (0.75 to 1.05)	0.86 (0.63 to 1.18)	0.73 (0.52 to 1.03)	0.95 (0.67 to 1.34)	0.87 (0.70 to 1.08)	0.93 (0.77 to 1.12)
Age group						
Age < 70 (n = 22,985)	0.97 (0.86 to 1.10)	1.09 (0.89 to 1.32)	0.88 (0.69 to 1.13)	1.20 (0.85 to 1.72)	0.95 (0.80 to 1.14)	1.04 (0.91 to 1.19)
Age ≥ 70 (n = 6,533)	1.04 (0.89 to 1.20)	1.10 (0.80 to 1.50)	0.78 (0.59 to 1.02)	1.16 (0.80 to 1.67)	1.02 (0.85 to 1.22)	1.01 (0.88 to 1.16)
BMI category						
BMI < 30 (n = 9,811)	1.06 (0.91 to 1.23)	1.23 (0.93 to 1.63)	0.78 (0.59 to 1.04)	1.52 (0.88 to 2.64)	1.07 (0.87 to 1.32)	1.03 (0.88 to 1.21)
BMI ≥ 30 (n = 19,707)	0.97 (0.87 to 1.09)	1.04 (0.85 to 1.28)	0.86 (0.70 to 1.06)	1.10 (0.83 to 1.46)	0.96 (0.82 to 1.12)	1.04 (0.92 to 1.17)
Subtypes of SU						
Gliclazide (n = 16,152)	1.01 (0.93 to 1.10)	1.12 (0.94 to 1.33)	0.85 (0.71 to 1.01)	1.18 (0.92 to 1.51)	1.00 (0.88 to 1.13)	1.04 (0.95 to 1.15)
Glimepiride (n = 1,540)	0.94 (0.77 to 1.16)	1.00 (0.67 to 1.50)	0.77 (0.47 to 1.25)	1.16 (0.69 to 1.95)	0.98 (0.75 to 1.28)	0.96 (0.77 to 1.19)
Glipizide (n = 818)	0.93 (0.75 to 1.16)	0.81 (0.50 to 1.32)	0.68 (0.40 to 1.14)	1.17 (0.63 to 2.18)	1.02 (0.77 to 1.35)	0.97 (0.77 to 1.22)
Glibenclamide* (n = 21)	(--)	(--)	(--)	(--)	(--)	(--)

*Hazard ratios for glibenclamide were not evaluated due to the extremely small sample size.

sTable 3. Comparison of outcome rates between sulphonylureas (SU) and DPP-4 inhibitors (DPP4i) in subgroups of cohort stratified by prior history of MACE, age, BMI, and subtypes of SU.

	4P-MACE	Hospitalization for MI	Hospitalization for stroke	Hospitalization for heart failure	Cardiovascular death	All-cause death
MACE history						
No prior MACE (n = 24,277)	1.02 (0.91 to 1.16)	1.14 (0.92 to 1.42)	0.85 (0.67 to 1.08)	1.28 (0.87 to 1.90)	1.05 (0.88 to 1.26)	1.03 (0.91 to 1.17)
Prior MACE (n = 3,444)	0.89 (0.75 to 1.06)	0.84 (0.60 to 1.18)	0.70 (0.48 to 1.01)	1.10 (0.74 to 1.63)	0.86 (0.68 to 1.09)	0.92 (0.75 to 1.12)
Age group						
Age < 70 (n = 21,436)	0.94 (0.82 to 1.07)	1.04 (0.83 to 1.31)	0.86 (0.66 to 1.14)	1.14 (0.77 to 1.69)	0.92 (0.75 to 1.12)	1.02 (0.87 to 1.18)
Age >= 70 (n = 6,209)	1.05 (0.89 to 1.23)	1.05 (0.75 to 1.46)	0.72 (0.53 to 0.97)	1.30 (0.85 to 1.97)	1.03 (0.84 to 1.26)	0.99 (0.85 to 1.16)
BMI category						
BMI < 30 (n = 9,245)	1.05 (0.88 to 1.25)	1.27 (0.92 to 1.76)	0.66 (0.48 to 0.91)	1.95 (0.94 to 4.06)	1.05 (0.83 to 1.34)	1.02 (0.85 to 1.22)
BMI >= 30 (n = 18,400)	0.95 (0.84 to 1.08)	0.97 (0.78 to 1.22)	0.88 (0.69 to 1.11)	1.07 (0.78 to 1.47)	0.96 (0.80 to 1.14)	1.01 (0.89 to 1.15)
Subtypes of SU						
Gliclazide (n = 16,152)	0.99 (0.89 to 1.09)	1.07 (0.88 to 1.30)	0.80 (0.66 to 0.97)	1.19 (0.90 to 1.57)	0.98 (0.85 to 1.13)	1.02 (0.92 to 1.14)
Glimepiride (n = 1,540)	0.95 (0.77 to 1.17)	0.98 (0.64 to 1.49)	0.71 (0.42 to 1.18)	1.28 (0.73 to 2.23)	0.99 (0.75 to 1.30)	0.93 (0.75 to 1.16)
Glipizide (n = 818)	0.91 (0.72 to 1.15)	0.76 (0.46 to 1.26)	0.62 (0.36 to 1.06)	1.33 (0.72 to 2.46)	1.02 (0.76 to 1.37)	0.95 (0.75 to 1.21)
Glibenclamide* (n = 21)	(--)	(--)	(--)	(--)	(--)	(--)

*Hazard ratios for glibenclamide were not evaluated due to the extremely small sample size.

sTable 4. Comparison of outcome rates between sulphonylureas (SU) and thiazolidinediones (TZD) in subgroups of cohort stratified by prior history of MACE, age, BMI, and subtypes of SU.

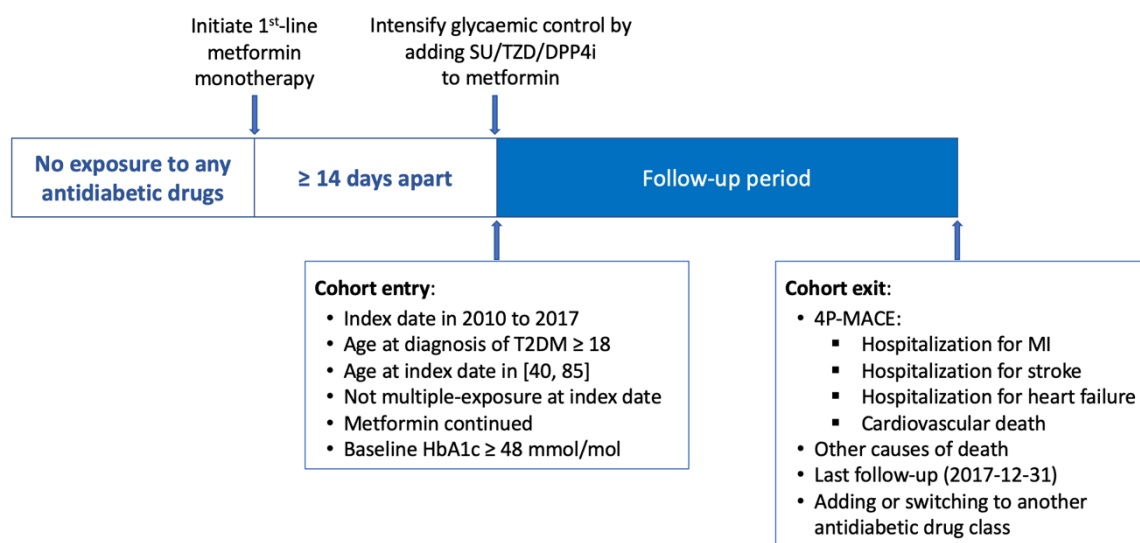
	4P-MACE	Hospitalization for MI	Hospitalization for stroke	Hospitalization for heart failure	Cardiovascular death	All-cause death
MACE history						
No prior MACE (n = 17,939)	1.11 (0.92 to 1.34)	1.32 (0.94 to 1.85)	1.01 (0.68 to 1.51)	1.55 (0.85 to 2.81)	1.07 (0.81 to 1.42)	1.10 (0.91 to 1.34)
Prior MACE (n = 2,465)	0.87 (0.60 to 1.28)	0.98 (0.48 to 2.01)	0.83 (0.39 to 1.76)	0.62 (0.31 to 1.24)	0.90 (0.56 to 1.44)	0.96 (0.64 to 1.42)
Age group						
Age < 70 (n = 15,753)	1.13 (0.93 to 1.37)	1.22 (0.86 to 1.73)	0.96 (0.61 to 1.51)	1.48 (0.81 to 2.70)	1.13 (0.84 to 1.52)	1.10 (0.87 to 1.40)
Age >= 70 (n = 4,651)	1.01 (0.76 to 1.34)	1.30 (0.69 to 2.44)	0.99 (0.58 to 1.71)	0.94 (0.52 to 1.72)	1.00 (0.71 to 1.40)	1.07 (0.82 to 1.39)
BMI category						
BMI < 30 (n = 7,314)	1.07 (0.81 to 1.41)	1.12 (0.68 to 1.84)	1.29 (0.69 to 2.39)	1.08 (0.49 to 2.41)	1.10 (0.76 to 1.61)	1.02 (0.77 to 1.36)
BMI >= 30 (n = 13,090)	1.09 (0.89 to 1.33)	1.35 (0.89 to 2.04)	0.85 (0.57 to 1.27)	1.24 (0.76 to 2.04)	1.05 (0.80 to 1.37)	1.15 (0.94 to 1.41)
Subtypes of SU						
Gliclazide (n = 16,152)	1.09 (0.93 to 1.29)	1.30 (0.95 to 1.77)	1.00 (0.70 to 1.43)	1.18 (0.76 to 1.81)	1.05 (0.84 to 1.32)	1.10 (0.93 to 1.30)
Glimepiride (n = 1,540)	0.94 (0.72 to 1.22)	1.13 (0.70 to 1.82)	0.90 (0.51 to 1.59)	1.12 (0.54 to 2.32)	0.89 (0.61 to 1.28)	0.96 (0.74 to 1.25)
Glipizide (n = 818)	1.10 (0.78 to 1.30)	1.06 (0.63 to 1.79)	0.88 (0.48 to 1.60)	0.95 (0.44 to 2.08)	1.10 (0.78 to 1.57)	1.02 (0.77 to 1.35)
Glibenclamide (n = 21)	(--)	(--)	(--)	(--)	(--)	(--)

*Hazard ratios for glibenclamide were not evaluated due to the extremely small sample size.

sMethod 2. Sensitivity analyses

In the sensitivity analyses, follow-up was additionally censored at adding or switching to a third class of antidiabetic medication (different from metformin and the second-line treatment currently received). Please see the sFigure 3 below for details.

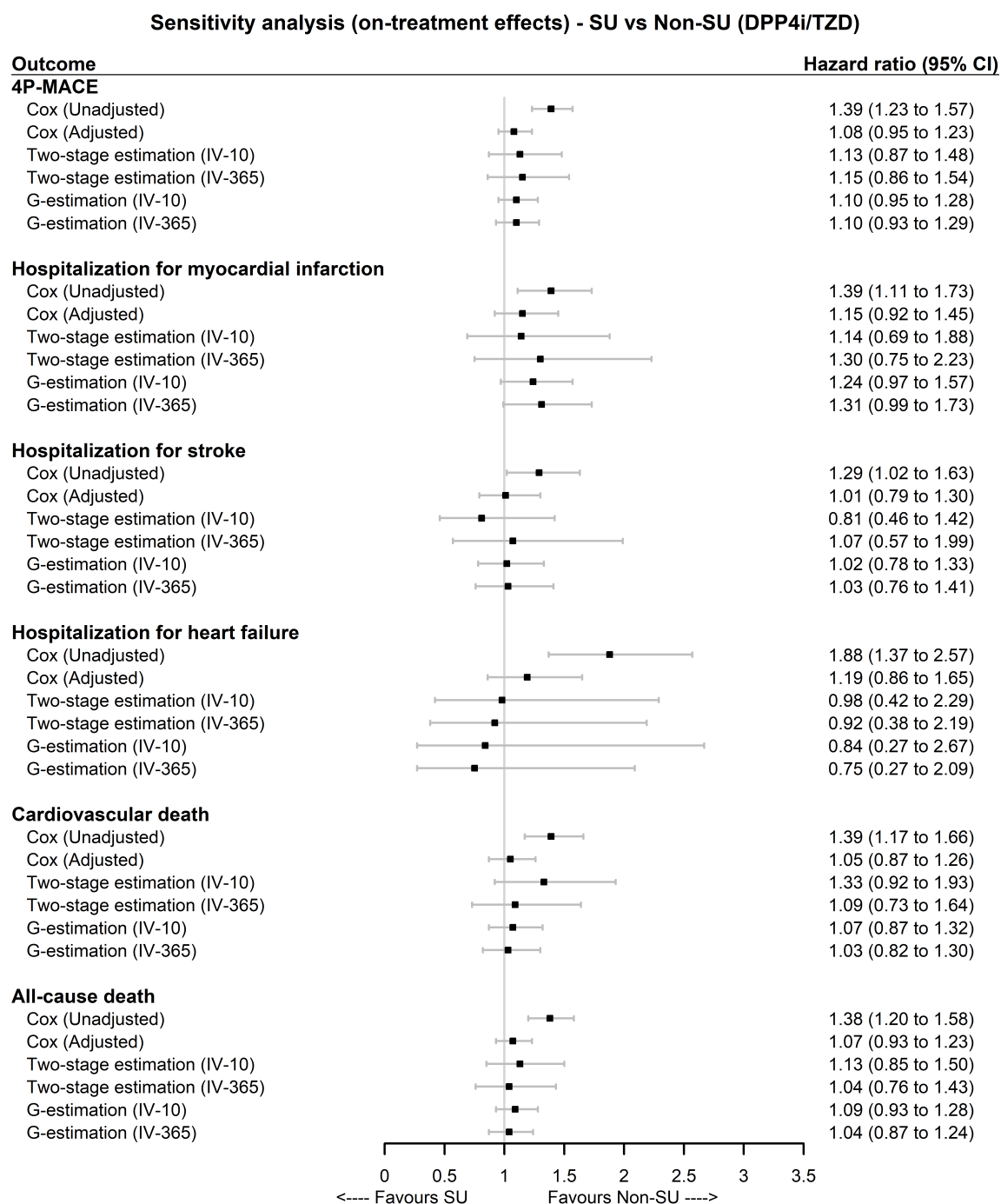
sFigure 5. Illustration of study design for the sensitivity analyses.



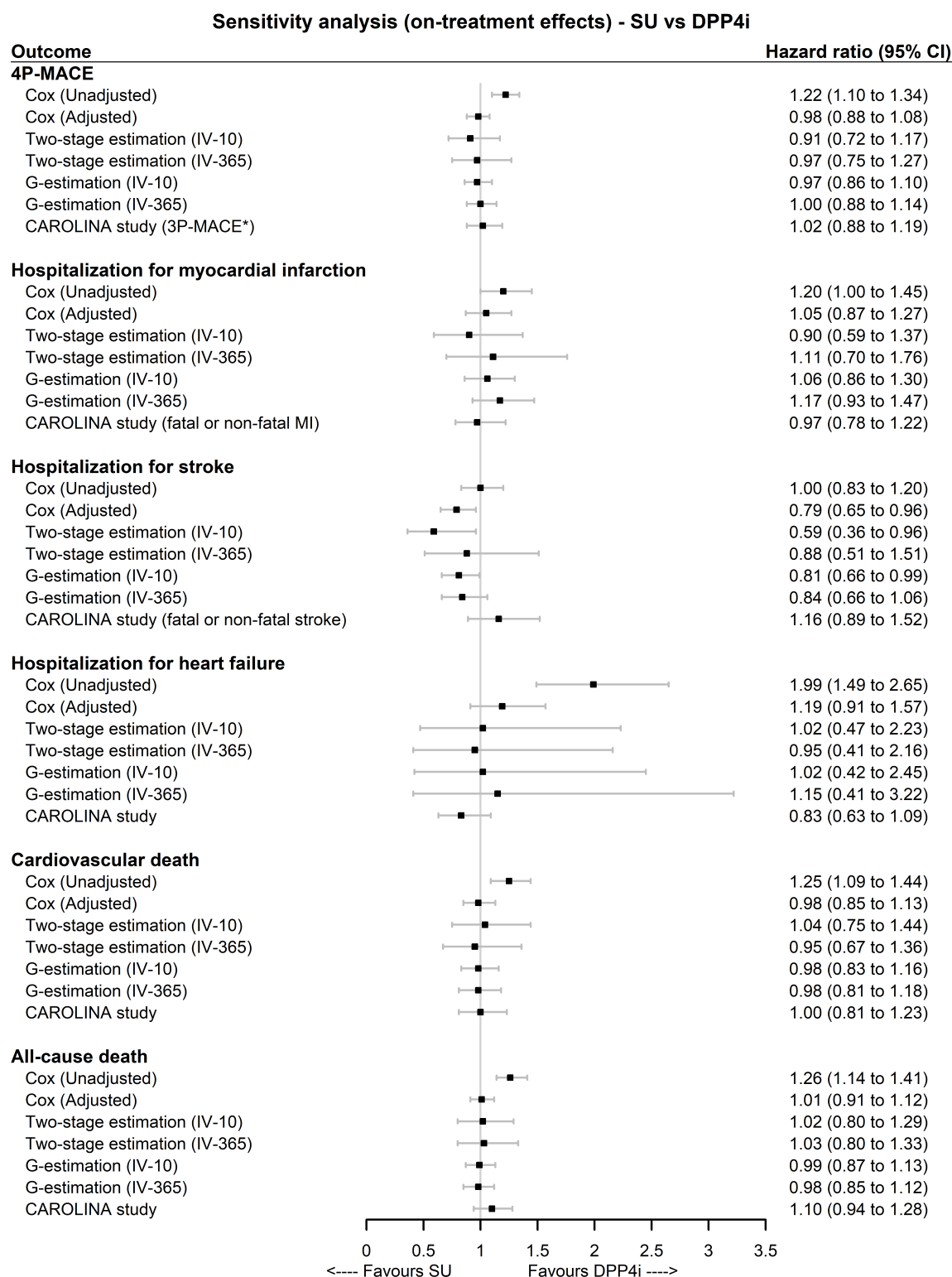
sTable 5. Incidence rates of study outcomes (follow up was additionally censored at adding or switching to a third class of antidiabetic medication).

	No. patients	No. events	Person years	Median (IQR) follow-up years	Incidence rate (95% CI) per 1000 person years
<u>4P-MACE</u>					
SU	18531	998	42623.9	1.8 (0.6 to 3.6)	23.4 (22.0 to 24.9)
Non-SU	10987	361	21793.9	1.4 (0.6 to 2.8)	16.6 (14.9 to 18.4)
DPP4i	9114	280	16625.7	1.3 (0.6 to 2.6)	16.8 (14.9 to 18.9)
TZD	1873	80	5168.3	2.1 (0.8 to 4.5)	15.5 (12.3 to 19.3)
<u>Hospitalization for MI</u>					
SU	18531	303	43236.8	1.9 (0.6 to 3.7)	7.0 (6.2 to 7.8)
Non-SU	10987	111	21999.6	1.4 (0.6 to 2.8)	5.0 (4.2 to 6.1)
DPP4i	9114	90	16775.1	1.3 (0.6 to 2.6)	5.4 (4.3 to 6.6)
TZD	1873	21	5224.5	2.1 (0.8 to 4.6)	4.0 (2.5 to 6.1)
<u>Hospitalization for stroke</u>					
SU	18531	223	43364.0	1.9 (0.6 to 3.7)	5.1 (4.5 to 5.9)
Non-SU	10987	86	21986.5	1.4 (0.6 to 2.8)	3.9 (3.1 to 4.8)
DPP4i	9114	69	16756.1	1.3 (0.6 to 2.6)	4.1 (3.2 to 5.2)
TZD	1873	17	5230.4	2.1 (0.8 to 4.6)	3.3 (1.9 to 5.2)
<u>Hospitalization for HF</u>					
SU	18531	176	43333.4	1.9 (0.6 to 3.7)	4.1 (3.5 to 4.7)
Non-SU	10987	50	22027.5	1.4 (0.6 to 2.8)	2.3 (1.7 to 3.0)
DPP4i	9114	35	16809.1	1.3 (0.6 to 2.6)	2.1 (1.5 to 2.9)
TZD	1873	15	5218.4	2.1 (0.8 to 4.6)	2.9 (1.6 to 4.7)
<u>Cardiovascular death</u>					
SU	18531	510	43701.3	1.9 (0.6 to 3.7)	11.7 (10.7 to 12.7)
Non-SU	10987	174	22121.6	1.4 (0.6 to 2.9)	7.9 (6.7 to 9.1)
DPP4i	9114	136	16867.0	1.3 (0.6 to 2.6)	8.1 (6.8 to 9.5)
TZD	1873	38	5254.6	2.1 (0.8 to 4.6)	7.2 (5.1 to 9.9)
<u>All-cause death</u>					
SU	18531	871	43701.3	1.9 (0.6 to 3.7)	19.9 (18.6 to 21.3)
Non-SU	10987	301	22121.6	1.4 (0.6 to 2.9)	13.6 (12.1 to 15.2)
DPP4i	9114	230	16867.0	1.3 (0.6 to 2.6)	13.6 (11.9 to 15.5)
TZD	1873	71	5254.6	2.1 (0.8 to 4.6)	13.5 (10.6 to 17.0)

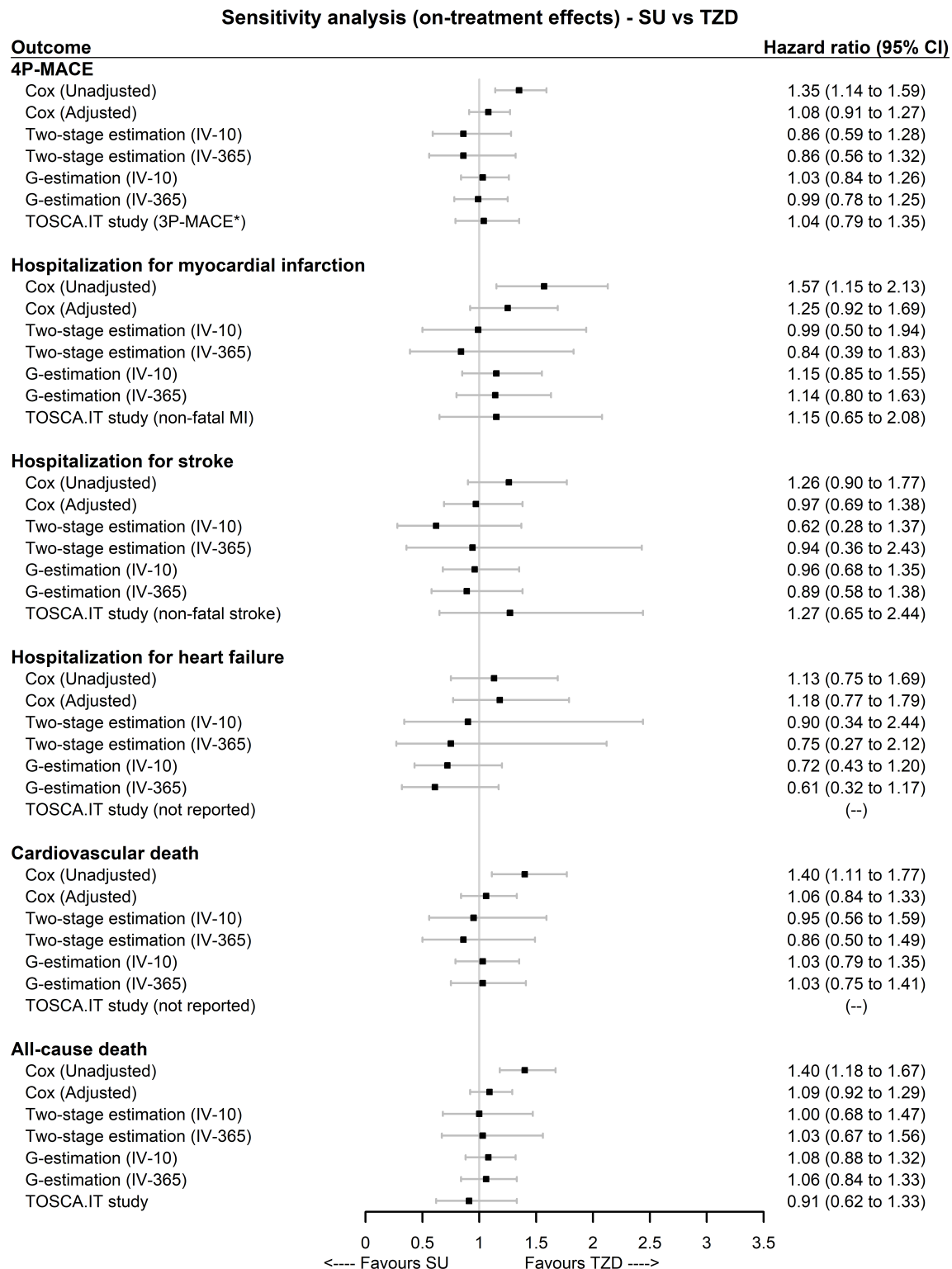
sFigure 6. Comparison of outcome rates between SU and non-SU agents (DPP4i or TZD).



sFigure 7. Comparison of outcome rates between SU and DPP4i.



sFigure 8. Comparison of outcome rates between SU and TZD.



sMethod 3. Assessment of instrumental variable (IV) conditions

The three essential IV conditions are: (i) 'Relevance' – the IV is associated with the exposure of interest; (ii) 'Exclusion restriction' – the IV does not affect the outcome except through its potential effect on the exposure; and (iii) 'Exchangeability' – the IV and the outcome have no common causes. For the proposed two IVs, condition (i) was tested under the two-stage setting by performing likelihood ratio test, analogous to reporting the partial F statistic for the linear framework. Point-biserial correlation was used to quantify the strength of the IVs. Moreover, logistic regression models were built with SU prescription as the outcome, regressing on the z-transformed IV with and without including year of cohort entry. The strength of the IV can be assured if the odds ratio of the z-transformed IV remains large with or without including year of cohort entry. Condition (ii) was assumed to be met because the prescribing preference at practice level was unlikely to affect a new patient's CV risk or mortality other than through the actual prescription issued. Condition (iii) was falsified by using the standardized difference (SDif), an intuitive measure for assessing covariates balance. If measured covariates are well balanced, it is reasonable to assume that such balance may also be achieved in the potential unmeasured confounders.(1) As our IVs are continuous proportions, the balance was assessed across the quartiles. The maximum SDif for each covariate was reported, with small values (e.g. < 0.1) indicating better balance.(2)

In addition to the three essential IV conditions above, obtaining a point estimate for the causal exposure effect requires a further fourth condition of either treatment effect homogeneity or monotonicity.(3) Here we assumed the monotonicity was established, that is, all study participants were assumed to comply with the preference of their practices. In other words, patients registered with a practice with stronger preference for a given drug would be more likely to receive that drug in comparison to the other drugs. Under this assumption, the estimated exposure effect would be interpreted as the average causal effect in those who complied with practice preference (also known as the local average treatment effect).

sTable 6. Assessment of IV condition (i): IV strength evaluated using likelihood ratio test and point biserial correlation.

Instrumental variable	Deviance of the first stage model ¹		Likelihood ratio test p value	Point-biserial correlation
	Without IV	With IV		
IV-10	35467	28829	< 0.001	0.497
IV-365	27111	21697	< 0.001	0.516

¹First stage model: Exposure to SU (yes/no) ~ Instrument (IV-10 or IV-365) + year of cohort entry.

sTable 7. Assessment of IV condition (i): IV strength evaluated using logistic regression.

Instrumental variable	Crude odds ratio ¹ (95% CI)	Adjusted odds ratio ² (95% CI)	p value (Wald's test)	p value (Likelihood ratio test)
IV-10	3.25 (3.15 – 3.36)	3.19 (3.09 – 3.29)	< 0.001	< 0.001
IV-365	3.45 (3.33 – 3.58)	3.39 (3.26 – 3.52)	< 0.001	< 0.001

¹Crude odds ratios were obtained from the univariate logistic model: Exposure to SU (yes/no) ~ z-transformed Instrument (IV-10 or IV-365).

²Adjusted odds ratios were obtained from the multivariate logistic model: Exposure to SU (yes/no) ~ z-transformed Instrument (IV-10 or IV-365) + year of cohort entry.

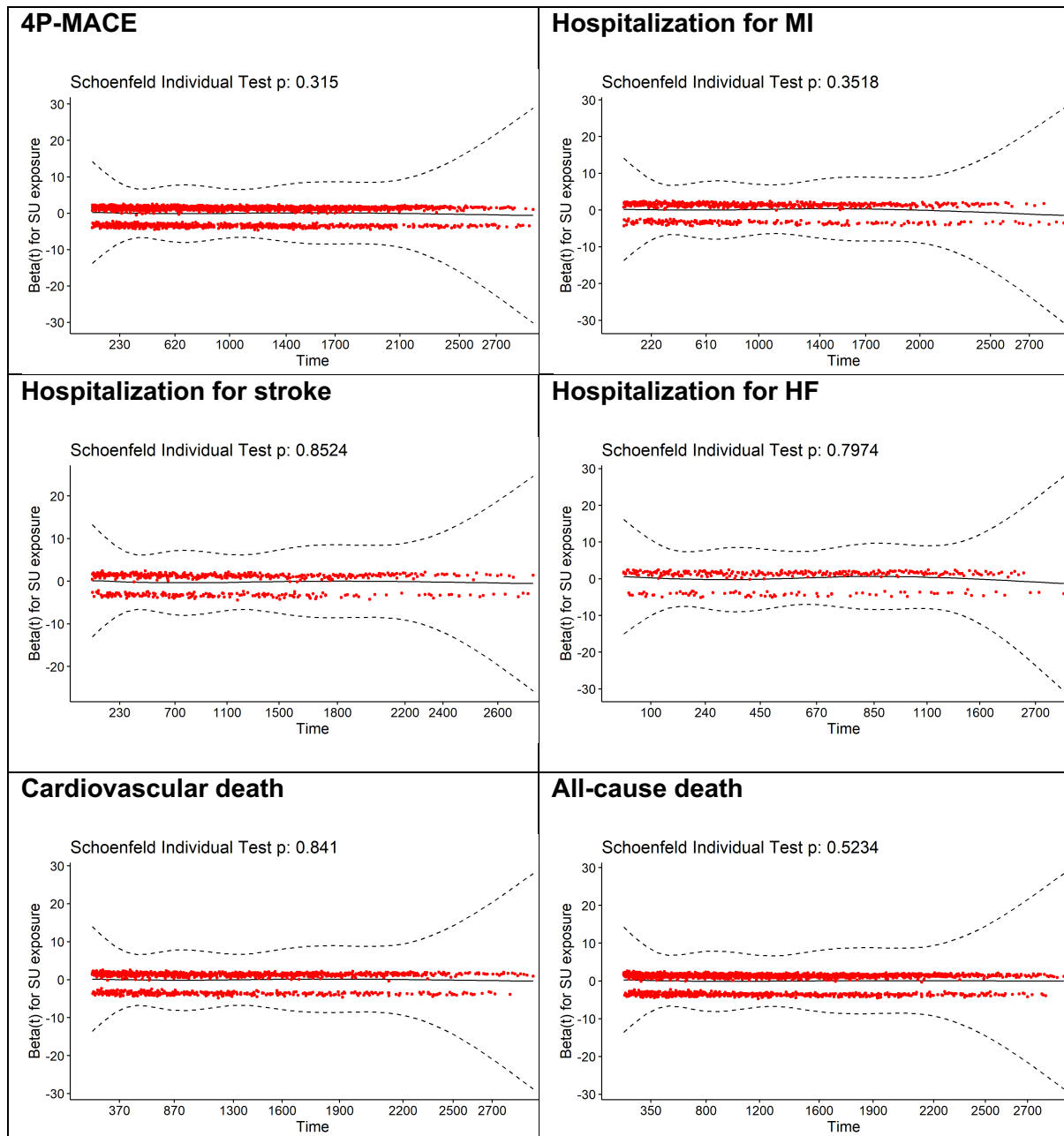
sTable 8. Falsification of IV condition (iii): assessing covariate balance.

	Standardised mean difference (SDif)	Maximum pairwise standardised mean difference (SDif) across IV quartiles	
Covariates	Exposure (SU vs non-SU)	IV-10	IV-365
Age	<u>0.105</u>	0.053	0.064
Sex	0.009	0.007	0.015
Ethnicity	0.022	0.053	0.041
Duration of diabetes	-0.014	0.029	0.051
HbA1c	<u>0.220</u>	0.098	0.097
Total cholesterol/HDL ratio	0.044	0.065	0.093
Systolic blood pressure	-0.012	0.044	0.071
Baseline eGFR (CKD-EPI)			
≥90	-0.011	0.033	0.037
60-89	0.006	0.027	0.019
45-59	0.004	0.004	0.015
<45	0.002	0.005	0.007
Body mass index (kg/m²)			
<25	0.032	0.003	0.008
25-29	0.053	0.009	0.013
30-34	-0.004	0.009	0.006
35-40	-0.031	0.010	0.008
≥40	-0.050	0.008	0.009
Smoking status			
Never	-0.026	0.009	0.012
Ever	-0.001	0.011	0.009
Current	0.027	0.017	0.017
SIMD quintile			
1	-0.011	0.029	0.023

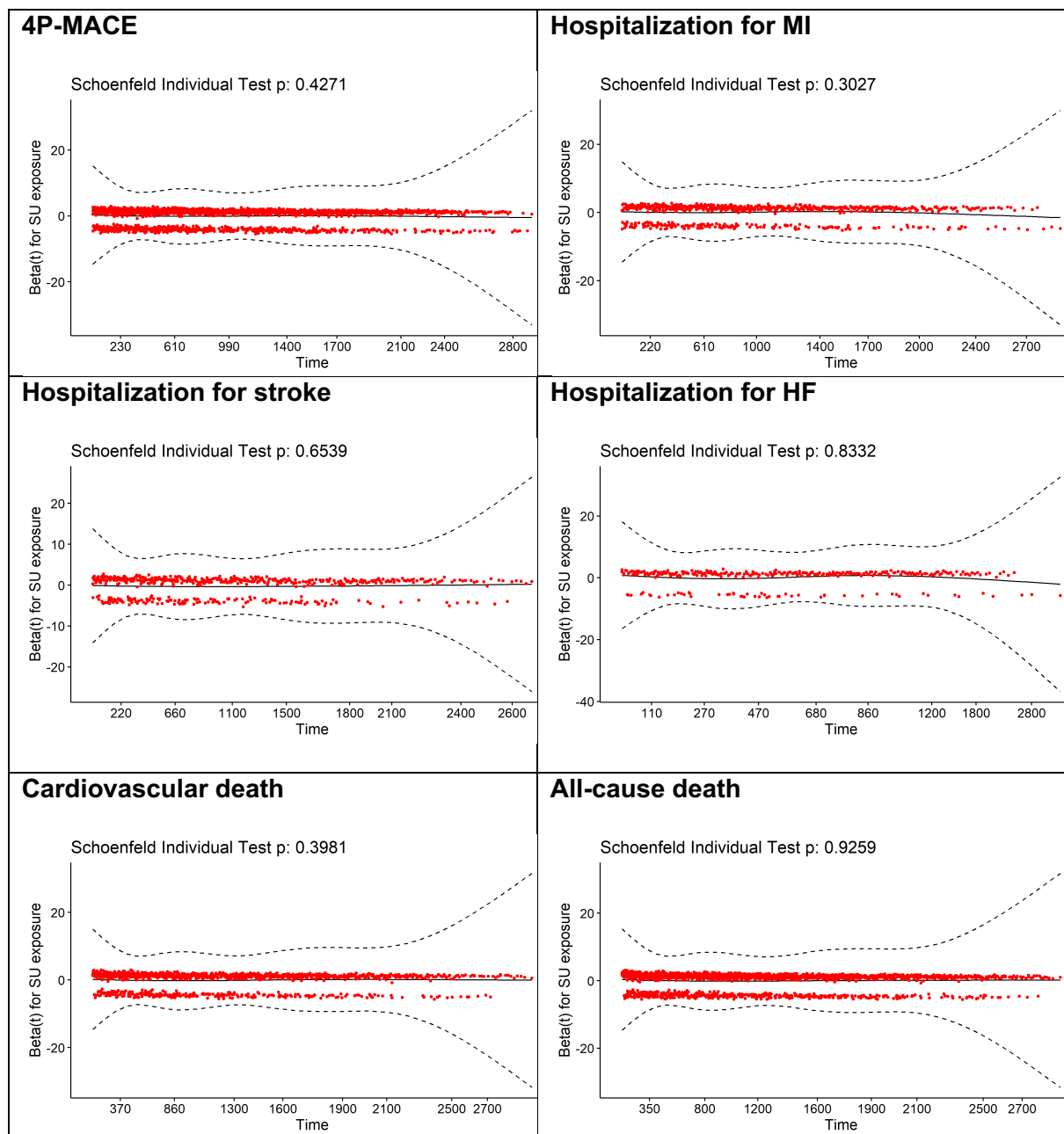
2	-0.012	0.023	0.020
3	0.008	0.026	0.005
4	0.006	0.015	0.020
5	0.010	0.014	0.017
History of conditions:			
Arterial fibrillations	0.009	0.004	0.003
Coronary artery disease	0.025	0.007	0.005
Cancer	0.018	0.008	0.011
COPD	0.013	0.008	0.014
Diabetic retinopathy	0.012	0.032	0.025
Hypertension (ICD-coded)	0.021	0.011	0.010
Myocardial infarction	0.011	0.009	0.002
Stroke	0.004	0.004	0.005
Heart failure	0.010	0.002	0.001
Currently used drugs:			
ACEis/ARBs	-0.021	0.014	0.009
Beta blockers	0.024	0.017	0.015
Calcium channel blockers	-0.004	0.011	0.024
Diuretics	0.013	0.008	0.009
Cardiac glycosides	0.006	0.003	0.005
Nitrates	0.011	0.002	0.003
Oral anticoagulants	0.005	0.004	0.004
Antiplatelets	0.041	0.031	0.026
Lipid lowering drugs	-0.008	0.009	0.010

sMethod 4. Assessment of proportional hazard assumptions

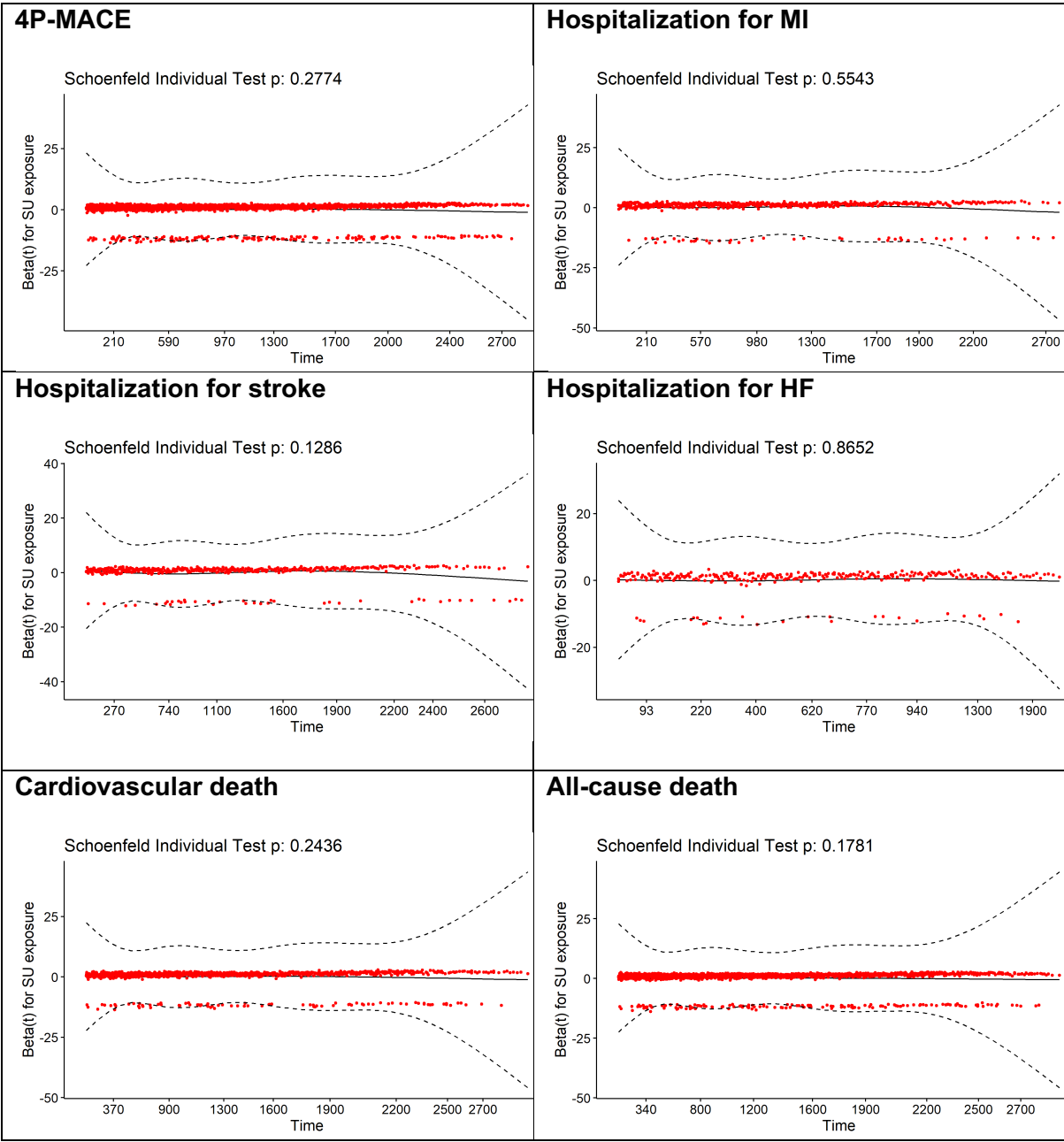
sTable 9. Plot of Schoenfeld residuals for the comparison between SU vs non-SU agents (DPP4i or TZD).



sTable 10. Plot of Schoenfeld residuals for the comparison between SU vs DPP4i.



sTable 11. Plot of Schoenfeld residuals for the comparison between SU vs TZD.



References

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3. Hernán MA RJ. *Causal Inference: What If.*: Boca Raton: Chapman & Hall/CRC; 2020.