Trends in timing of and glycemia at initiation of second-line type 2 diabetes treatment in US adults

Supplemental Table 1. Medication names included in defining cohort of individuals included in this study.

Metformin	Metformin, Glucophage, Fortamet, Glumetza, Riomet, Janumet (combination)
Sulfonylurea	Acetohexamide, Glyburide, Glibenclamide, Glimepiride, Tolbutamide, Glipizide, Chlorpropamide, Tolazamide, Amaryl, Glucotrol,
Insulin	Insulin, Aspart, Humulin, Glargine, Detemir, Lantus, Levemir, Novolog, Novolin, NPH, Regular
Thiazolidinedione	Pioglitazone, Actos, Rosiglitazone, Avandia, Troglitazone
DPP-4i	Alogliptin, Saxagliptin, Sitagliptin, Linagliptin, Januvia, Onglyza, Tradjenta, Nesina, Janumet (combination)
GLP1-RA	Liraglutide, Exenatide, Semaglutide, Lixisenatide, Albiglutide, Dulaglutide, Byetta, Bydureon, Victoza, Saxenda, Adlyxin, Tanzeum, Trulicity, Ozempic
SGLT-2i	Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin, Invokana, Farxiga, Jardiance, Steglatro
Meglitinide	Repaglinide, Prandin, Nateglinide

Supplemental Table 2. Distribution of medication classes used for initial diabetes monotherapy from 2005 to 2013.

Drug class		Total	Diabetes monotherapy initiation year								
			2005	2006	2007	2008	2009	2010	2011	2012	2013
Metformin	N	206,841	18,206	20,997	22,957	23,306	23,542	24,138	25,366	23,931	24,398
	%	70.7%	55.1%	59.7%	66.1%	70.3%	73.3%	75.9%	77.8%	79.8%	81.8%
Sulfonylurea	N	66,522	12,134	11,539	9510	7757	6575	5725	5328	4275	3679
	%	22.7%	36.7%	32.8%	27.4%	23.4%	20.5%	18.0%	16.3%	14.3%	12.3%
Insulin	N	13,241	1245	1274	1320	1527	1594	1590	1648	1511	1532
	%	4.5%	3.8%	3.6%	3.8%	4.6%	5.0%	5.0%	5.1%	5.0%	5.1%
TZD	N	4304	1399	1298	792	309	206	169	79	31	21
	%	1.5%	4.2%	3.7%	2.3%	0.9%	0.6%	0.5%	0.2%	0.1%	0.1%
DPP-4i	N	1093	0	1	87	157	170	134	167	201	176
	%	0.4%	0.0%	0.0%	0.3%	0.5%	0.5%	0.4%	0.5%	0.7%	0.6%
Meglitinide	N	394	71	80	67	59	36	27	18	25	11
	%	0.1%	0.2%	0.2%	0.2%	0.2%	0.1%	0.1%	0.1%	0.1%	0.0%
GLP1-RA	N	117	0	11	23	23	11	8	14	10	17
	%	0.0%	0.0%	0.0%	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.1%
SGLT-2i	N	1	0	0	0	0	0	0	0	0	1
	%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Abbreviations: TZD, Thiazolidinedione; DPP-4i, Dipeptidyl peptidase 4 inhibitor; GLP1-RA, glucagon-like peptide 1 receptor agonist; SGLT-2i, Sodium glucose cotransporter 2 inhibitor

Supplemental Table 3. Rates of missing data for variables included in multivariable models.

	Percent Missing
Age	0
Sex	0
Race	0
Smoking Status	0.1
BMI	0
HbA1c	3.7
eGFR	1.9
Creatinine	1.9
Comorbidities	
Cancer	0
Coronary Artery Disease	0
Congestive Heart Failure	0
Stroke	0
Kidney Disease	0
Liver Disease	0
COPD	0

Supplemental Table 4. Comorbidities at baseline across years of metformin monotherapy initiation.

	Total	2005	2006	2007	2008	2009	2010	2011	2012	2013	P_{het}*	P_{trend}†
Metformin start year												
Cancer, No. (%)	68,925 (34.6)	4927 (28.2)	6201 (30.6)	7146 (32.4)	7672 (34.2)	8093 (35.8)	8461 (36.5)	8986 (36.7)	8578 (37.2)	8861 (37.7)	<0.0001	<0.0001
Coronary Artery Disease, No. (%)	56,216 (28.2)	5404 (31.0)	6126 (30.3)	6672 (30.2)	6788 (30.3)	6410 (28.4)	6353 (27.4)	6563 (26.8)	6040 (26.2)	5860 (24.9)	<0.0001	1
Congestive Heart Failure, No. (%)	11,052 (5.6)	1011 (5.8)	1128 (5.6)	1221 (5.5)	1309 (5.8)	1246 (5.5)	1205 (5.2)	1352 (5.5)	1351 (5.9)	1229 (5.2)	0.1	1
Stroke, No. (%)	16,076 (8.1)	1304 (7.5)	1554 (7.7)	1809 (8.2)	1863 (8.3)	1850 (8.2)	1881 (8.1)	1992 (8.1)	1935 (8.4)	1888 (8.0)	0.01	0.006
Kidney Disease, No. (%)	511 (0.3)	15 (0.1)	50 (0.2)	69 (0.3)	72 (0.3)	74 (0.3)	77 (0.3)	48 (0.2)	55 (0.2)	51 (0.2)	0.7	0.3
Liver Disease, No. (%)	4152 (2.1)	202 (1.2)	311 (1.5)	375 (1.7)	430 (1.9)	471 (2.1)	523 (2.3)	561 (2.3)	609 (2.6)	670 (2.8)	<0.0001	<0.0001
Chronic Obstructive Pulmonary Disease, No. (%)	41,688 (20.9)	3483 (20.0)	4144 (20.5)	4533 (20.5)	4813 (21.5)	4783 (21.2)	4885 (21.1)	5234 (21.4)	4846 (21.0)	4967 (21.1)	0.001	0.0006

* Cochran Armitage Test for directional trend for increasing or decreasing prevalence across years of metformin initiation
† Cochran Armitage Test for directional trend for increasing prevalence across metformin initiation years

Supplemental Table 5. Comparison of characteristics of individuals with less than versus at least 5 years of follow-up.

	<5 years of follow-up	≥5 years of follow-up
	N=50,169	N=148,873
Age (years), median [IQR]	65.96 [58.77, 75.54]	61.77 [55.66, 67.16]
Male sex, No. (%)	48536 (96.7)	142173 (95.5)
Race, No. (%)		
BLACK	6294 (12.5)	24641 (16.6)
HISPANIC	2310 (4.6)	9175 (6.2)
OTHER	7356 (14.7)	11467 (7.7)
WHITE	34209 (68.2)	103590 (69.6)
Smoking status, No. (%)		
MISSING	31 (0.1)	85 (0.1)
CURRENT	14861 (29.6)	43119 (29.0)
FORMER	24447 (48.7)	70170 (47.1)
NEVER	10830 (21.6)	35499 (23.8)
BMI (kg/m^2), median [IQR]	31.47 [27.83, 35.74]	32.81 [29.34, 37.02]
SBP (mmHg), median [IQR]	132.00 [122.00, 141.00]	132.00 [122.00, 140.00]
DBP, (mmHg) median [IQR]	76.00 [68.00, 83.00]	78.00 [70.00, 84.00]
HDL (mg/dL), median [IQR]	38.00 [32.00, 45.40]	38.00 [32.00, 44.00]
LDL (mg/dL), median [IQR]	95.00 [75.00, 120.00]	98.00 [78.20, 122.90]
TC (mg/dL), median [IQR]	169.00 [145.00, 199.00]	173.00 [149.00, 202.00]
TG (mg/dL), median [IQR]	154.00 [107.00, 228.00]	165.00 [114.00, 243.00]
FPG (mg/dL), median [IQR]	136.00 [116.00, 166.00]	137.00 [119.00, 166.00]
HbA1c (%), median [IQR]	6.90 [6.40, 7.60]	7.00 [6.50, 7.70]
eGFR (mL/min/1.73m^2), median [IQR]	75.40 [64.60, 88.72]	77.53 [67.58, 90.50]
Serum creatinine (mg/dL), median [IQR]	1.00 [0.90, 1.14]	1.00 [0.90, 1.10]
Cancer, No. (%)	17,103 (34.1)	51,822 (34.8)
Coronary Artery Disease, No. (%)	16,856 (33.6)	39,360 (26.4)
Congestive Heart Failure, No. (%)	4456 (8.9)	6596 (4.4)
Stroke, No. (%)	5282 (10.5)	10,794 (7.3)
Kidney Disease, No. (%)	183 (0.4)	328 (0.2)
Liver Disease, No. (%)	958 (1.9)	3194 (2.1)
COPD, No. (%)	12,573 (25.1)	29,115 (19.6)
Follow-up time (weeks), median [IQR]	157.29 [68.71, 225.29]	275.14 [267.43, 285.57]

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate.

Supplemental Table 6. Hemoglobin A1c trends at initiation of metformin monotherapy and second medication stratifying at age 50 years, 60 years, and 65 years.

Age strata	HbA1c timepoint	Metformin monotherapy initiation year									Trend P^*
		2005	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	
≤50 years	**Metformin start, % (SD)**	7.61 (1.77)	7.67 (1.75)	7.66 (1.76)	7.61 (1.70)	7.60 (1.60)	7.66 (1.72)	7.71 (1.69)	7.73 (1.67)	7.69 (1.58)	0.89
	2nd Med start, % (SD)	8.56 (2.03)	8.55 (1.89)	8.55 (1.92)	8.70 (1.99)	8.74 (1.90)	8.96 (1.94)	9.12 (2.00)	9.15 (2.05)	9.19 (2.03)	<0.0001
>50 years	**Metformin start, % (SD)**	7.21 (1.42)	7.20 (1.35)	7.15 (1.33)	7.14 (1.31)	7.18 (1.31)	7.22 (1.29)	7.29 (1.29)	7.31 (1.31)	7.32 (1.28)	<0.0001
	2nd Med start, % (SD)	7.61 (1.55)	7.66 (1.59)	7.71 (1.61)	7.80 (1.65)	7.99 (1.72)	8.13 (1.77)	8.21 (1.81)	8.29 (1.84)	8.40 (1.86)	<0.0001
≤60 years	**Metformin start, % (SD)**	7.45 (1.66)	7.44 (1.59)	7.43 (1.62)	7.42 (1.58)	7.47 (1.53)	7.52 (1.57)	7.58 (1.57)	7.57 (1.54)	7.57 (1.50)	0.0006
	2nd Med start, % (SD)	8.12 (1.81)	8.16 (1.79)	8.19 (1.79)	8.36 (1.90)	8.53 (1.88)	8.72 (1.94)	8.83 (1.98)	8.90 (2.01)	8.98 (1.99)	<0.0001
>60 years	**Metformin start, % (SD)**	7.10 (1.25)	7.10 (1.23)	7.04 (1.18)	7.04 (1.19)	7.09 (1.20)	7.14 (1.20)	7.21 (1.20)	7.25 (1.25)	7.25 (1.20)	<0.0001
	2nd Med start, % (SD)	7.33 (1.36)	7.40 (1.41)	7.47 (1.48)	7.56 (1.48)	7.75 (1.59)	7.89 (1.63)	7.99 (1.70)	8.07 (1.73)	8.17 (1.77)	<0.0001
≤65 years	**Metformin start, % (SD)**	7.41 (1.62)	7.39 (1.54)	7.35 (1.53)	7.31 (1.49)	7.35 (1.45)	7.40 (1.47)	7.46 (1.46)	7.47 (1.46)	7.49 (1.43)	<0.0001
	2nd Med start, % (SD)	8.02 (1.77)	8.04 (1.75)	8.06 (1.75)	8.18 (1.82)	8.34 (1.83)	8.49 (1.88)	8.58 (1.92)	8.70 (1.95)	8.80 (1.96)	<0.0001
>65 years	**Metformin start, % (SD)**	7.02 (1.15)	7.03 (1.13)	6.96 (1.07)	6.97 (1.09)	7.02 (1.12)	7.05 (1.07)	7.14 (1.12)	7.19 (1.18)	7.20 (1.15)	<0.0001
	2nd Med start, % (SD)	7.17 (1.22)	7.22 (1.27)	7.24 (1.33)	7.33 (1.33)	7.46 (1.43)	7.62 (1.49)	7.79 (1.61)	7.85 (1.65)	8.02 (1.71)	<0.0001

* Adjusted models included sex, race, and baseline age, HbA1c, creatinine, and BMI.

Supplemental Table 7. Hemoglobin A1c trends at the end of follow-up among all participants, those receiving second line diabetes treatment within five years, and those remaining on metformin monotherapy.

	Metformin start year									Trend P-value*
	2005	2006	2007	2008	2009	2010	2011	2012	2013	
All participants										
Mean HbA1c, % (SD)	6.94 (1.28)	6.97 (1.31)	6.97 (1.33)	7.00 (1.35)	7.03 (1.39)	7.02 (1.39)	7.03 (1.41)	7.05 (1.42)	7.09 (1.42)	<0.0001
HbA1c < 7, No. (%)	10,768 (61.9)	12,422 (61.6)	13,667 (62.0)	13,591 (60.7)	13,590 (60.3)	14,019 (60.5)	14,847 (60.7)	13,810 (59.9)	13,788 (58.6)	
7 ≤ HbA1c < 8, No. (%)	3,800 (21.9)	4,358 (21.6)	4,695 (21.3)	4,959 (22.1)	4,839 (21.5)	5,073 (21.9)	5,235 (21.4)	4,969 (21.5)	5,242 (22.3)	
8 ≤ HbA1c < 9, No. (%)	1,297 (7.5)	1,540 (7.6)	1,676 (7.6)	1,807 (8.1)	1,910 (8.5)	1,868 (8.1)	1,998 (8.2)	1,984 (8.6)	2,095 (8.9)	
HbA1c ≥ 9, No. (%)	1,206 (6.9)	1,536 (7.6)	1,681 (7.6)	1,772 (7.9)	1,960 (8.7)	1,992 (8.6)	2,206 (9.0)	2,121 (9.2)	2,204 (9.4)	
Received 2nd line drug										
Mean HbA1c, % (SD)	7.25 (1.39)	7.34 (1.45)	7.37 (1.48)	7.46 (1.52)	7.54 (1.57)	7.57 (1.58)	7.65 (1.63)	7.72 (1.66)	7.80 (1.68)	<0.0001
HbA1c < 7, No. (%)	5,728 (51.2)	6,029 (48.6)	6,199 (47.8)	5,547 (44.3)	5,248 (42.7)	5,015 (41.5)	4,689 (39.4)	3,922 (37.4)	3,572 (35.5)	
7 ≤ HbA1c < 8, No. (%)	3,115 (27.9)	3,480 (28.0)	3,626 (27.9)	3,655 (29.2)	3,506 (28.5)	3,550 (29.4)	3,473 (29.2)	3,048 (29.0)	2,914 (28.9)	
8 ≤ HbA1c < 9, No. (%)	1,191 (10.7)	1,430 (11.5)	1,556 (12.0)	1,647 (13.1)	1,702 (13.8)	1,637 (13.5)	1,705 (14.3)	1,602 (15.3)	1,613 (16.0)	
HbA1c ≥ 9, No. (%)	1,146 (10.3)	1,471 (11.9)	1,597 (12.3)	1,682 (13.4)	1,843 (15.0)	1,893 (15.7)	2,039 (17.1)	1,924 (18.3)	1,978 (19.6)	
No 2nd line drug										
Mean HbA1c, % (SD)	6.37 (0.76)	6.36 (0.71)	6.36 (0.73)	6.40 (0.75)	6.40 (0.77)	6.40 (0.78)	6.44 (0.81)	6.49 (0.84)	6.55 (0.87)	<0.0001
HbA1c < 7, No. (%)	5,675 (85.6)	7,228 (85.9)	8,468 (85.4)	9,193 (83.8)	9,717 (83.4)	10,598 (82.9)	12,057 (82.1)	11,764 (79.8)	12,314 (77.1)	
7 ≤ HbA1c < 8, No. (%)	793 (11.6)	1,052 (11.8)	1,254 (12.2)	1,518 (13.6)	1,603 (13.3)	1,824 (14.0)	2,125 (14.2)	2,337 (15.5)	2,848 (17.6)	
8 ≤ HbA1c < 9, No. (%)	130 (1.8)	160 (1.5)	146 (1.4)	192 (1.7)	270 (2.1)	278 (2.1)	355 (2.4)	449 (3.1)	588 (3.6)	
HbA1c ≥ 9, No. (%)	74 (1.0)	82 (0.9)	104 (1.0)	124 (0.9)	136 (1.2)	143 (0.9)	228 (1.4)	248 (1.6)	299 (1.7)	

* Adjusted models included sex, race, and baseline age, HbA1c, creatinine, and BMI.

Supplemental Table 8. Impact of additional covariates on temporal trends of second line diabetes medication initiation.

		Metformin monotherapy initiation year								
		2005	2006	2007	2008	2009	2010	2011	2012	2013
Model 1*	Hazard Ratio	REF	0.90	0.87	0.82	0.81	0.75	0.70	0.67	0.68
	(95% CI)		(0.87, 0.92)	(0.84, 0.90)	(0.80, 0.85)	(0.78, 0.83)	(0.73, 0.77)	(0.68, 0.72)	(0.65, 0.69)	(0.66, 0.70)
	P value	-	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Model 2†	Hazard Ratio	REF	0.89	0.87	0.82	0.81	0.75	0.70	0.67	0.68
	(95% CI)		(0.87, 0.92)	(0.84, 0.90)	(0.79, 0.84)	(0.78, 0.83)	(0.73, 0.77)	(0.68, 0.72)	(0.65, 0.69)	(0.66, 0.70)
	P value	-	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

* Model1: age, sex, race, HbA1c, creatinine, BMI, and smoking status

† Model 2: Model 1, plus history of coronary artery disease, stroke, congestive heart failure, kidney disease, liver disease, chronic obstructive pulmonary disease, cancer

Supplemental Table 9. Temporal trends in second line diabetes medication initiation in consecutive annual cohorts of metformin monotherapy initiators from 2005 to 2013, stratified by baseline cancer status.

|		Metformin monotherapy initiation year									
		2005	2006	2007	2008	2009	2010	2011	2012	2013	$P_{interaction}$
Without cancer	Hazard Ratio* (95% CI)	REF	0.89 (0.86, 0.92)	0.85 (0.82, 0.88)	0.82 (0.79, 0.85)	0.80 (0.77, 0.83)	0.74 (0.72, 0.77)	0.69 (0.66, 0.71)	0.66 (0.64, 0.69)	0.67 (0.65, 0.70)	
	P value	-	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.5
With cancer	Hazard Ratio* (95% CI)	REF	0.92 (0.87, 0.97)	0.92 (0.87, 0.90)	0.84 (0.79, 0.89)	0.85 (0.80, 0.90)	0.77 (0.73, 0.82)	0.73 (0.69, 0.77)	0.70 (0.66, 0.74)	0.70 (0.66, 0.74)	
	P value	-	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	

* Multivariable Cox proportional hazards model adjusted for age, sex, and baseline race, HbA1c, creatinine, and BMI

Supplemental Table 10. Hazard ratios for association of metformin initiation year with initiation of a second diabetes medication over 5 years, stratifying at age 50 years, 60 years, and 65 years.

| Age strata		Metformin monotherapy initiation year									$P_{interaction}$
		2005	2006	2007	2008	2009	2010	2011	2012	2013	
≤50 years	Hazard Ratio* (95% CI)	REF	0.94 (0.87, 1.02)	0.91 (0.83, 0.99)	0.91 (0.84, 0.98)	0.94 (0.87, 1.02)	0.80 (0.74, 0.87)	0.79 (0.73, 0.86)	0.79 (0.73, 0.86)	0.82 (0.75, 0.88)	<0.0001
	P value	-	0.16	0.02	0.02	0.12	<0.0001	<0.0001	<0.0001	<0.0001	
>50 years	Hazard Ratio* (95% CI)	REF	0.89 (0.86, 0.92)	0.87 (0.84, 0.90)	0.81 (0.79, 0.84)	0.79 (0.77, 0.82)	0.75 (0.72, 0.77)	0.69 (0.67, 0.71)	0.65 (0.63, 0.68)	0.66 (0.64, 0.68)	
	P value	-	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
≤60 years	Hazard Ratio* (95% CI)	REF	0.90 (0.86, 0.94)	0.89 (0.86, 0.93)	0.86 (0.82, 0.90)	0.86 (0.82, 0.89)	0.81 (0.78, 0.85)	0.75 (0.72, 0.78)	0.73 (0.70, 0.77)	0.75 (0.71, 0.78)	<0.0001
	P value	-	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
>60 years	Hazard Ratio* (95% CI)	REF	0.89 (0.85, 0.93)	0.85 (0.82, 0.89)	0.79 (0.76, 0.83)	0.78 (0.74, 0.81)	0.71 (0.68, 0.74)	0.66 (0.64, 0.69)	0.63 (0.60, 0.66)	0.63 (0.60, 0.66)	
	P value	-	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
≤65 years	Hazard Ratio* (95% CI)	REF	0.91 (0.87, 0.94)	0.90 (0.87, 0.93)	0.85 (0.82, 0.89)	0.86 (0.83, 0.89)	0.80 (0.77, 0.82)	0.73 (0.71, 0.76)	0.71 (0.69, 0.74)	0.73 (0.70, 0.76)	<0.0001
	P value	-	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
>65 years	Hazard Ratio* (95% CI)	REF	0.87 (0.83, 0.92)	0.81 (0.76, 0.85)	0.76 (0.72, 0.81)	0.71 (0.67, 0.75)	0.65 (0.61, 0.69)	0.63 (0.60, 0.67)	0.59 (0.56, 0.62)	0.59 (0.56, 0.63)	
	P value	-	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	

* Adjusted models included sex, race, and baseline age, HbA1c, creatinine, and BMI.

Supplemental Figure 1. Analysis of residuals for linear regression examining association of year of metformin monotherapy initiation with HbA1c at second-line medication initiation.
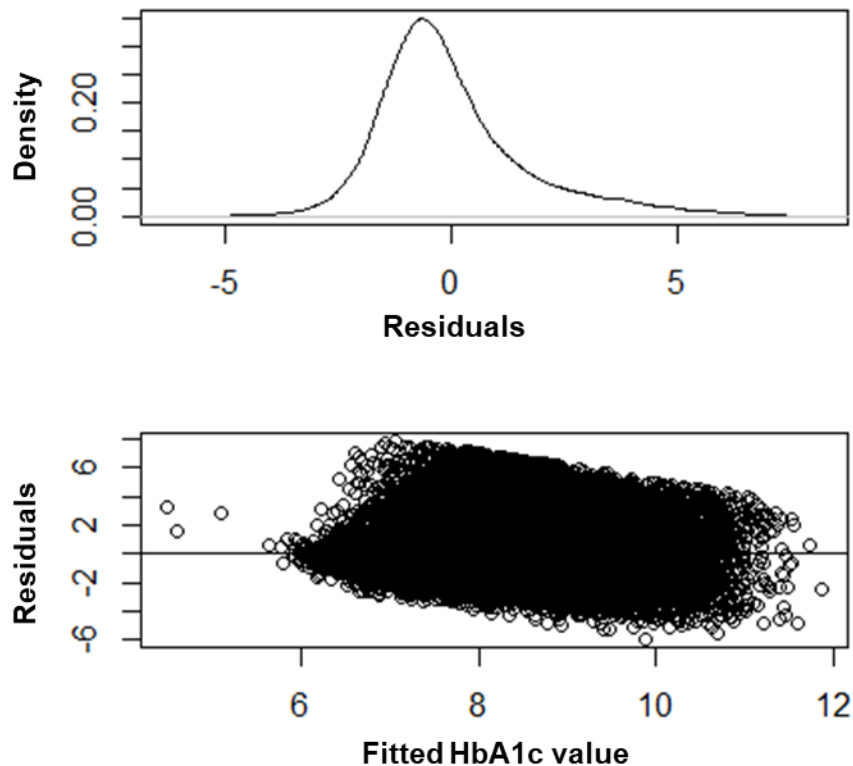

Supplemental Figure 1. Analysis of residuals for regression of year of metformin initiation with HbA1c at second-line diabetes treatment initiation. Top shows histogram density plot of residuals, demonstrating approximate normality in distribution of residuals. Bottom shows residuals as a function of fitted HbA1c value, demonstrating relative homogeneity of residuals across the fitted HbA1c distribution.

Supplemental Figure 2. Plot of Schoenfeld residuals assessing proportional hazards assumption when assessing association of year of metformin monotherapy initiation with time to second-line diabetes treatment initiation.
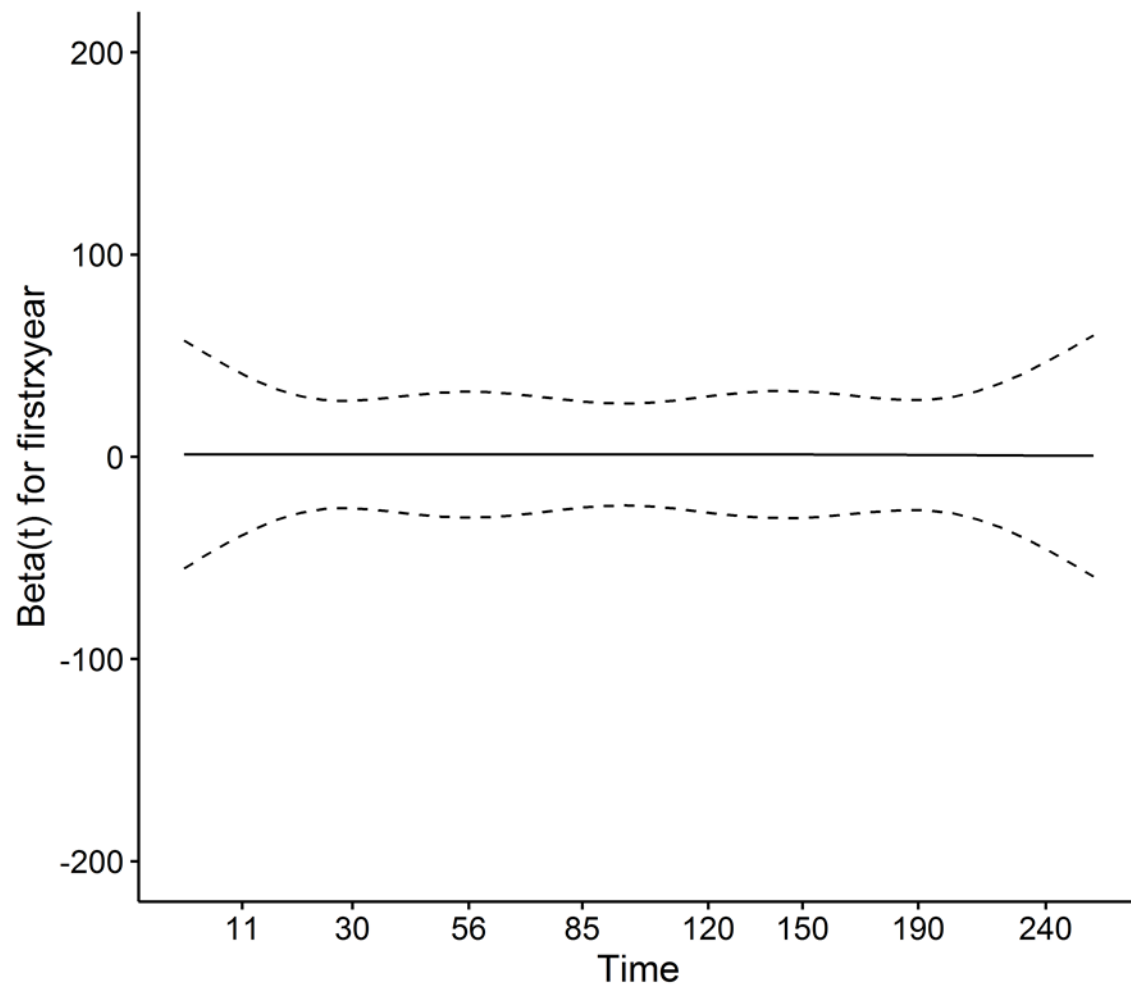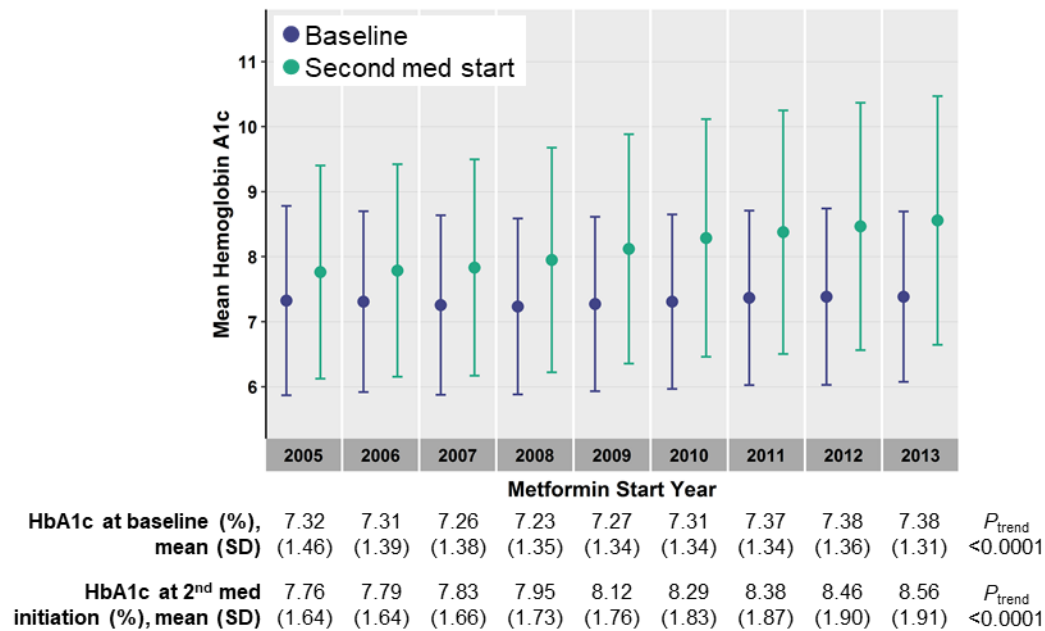

Supplemental Figure 2. Plot of Schoenfeld residuals versus time from Cox proportional hazards model evaluating association of year of metformin initiation with time to second-line diabetes treatment initiation. Solid line represents best fit line, and dashed lines represent 2 standard error confidence limits. Individual points not included due to number of observations. Visually, best fit line has slope near 0, but *P<0.0001* for test of independence of residuals with time.

Supplemental Figure 3. Trends in second-line diabetes medication use among patients receiving initial metformin monotherapy for diabetes from 2005-2013.
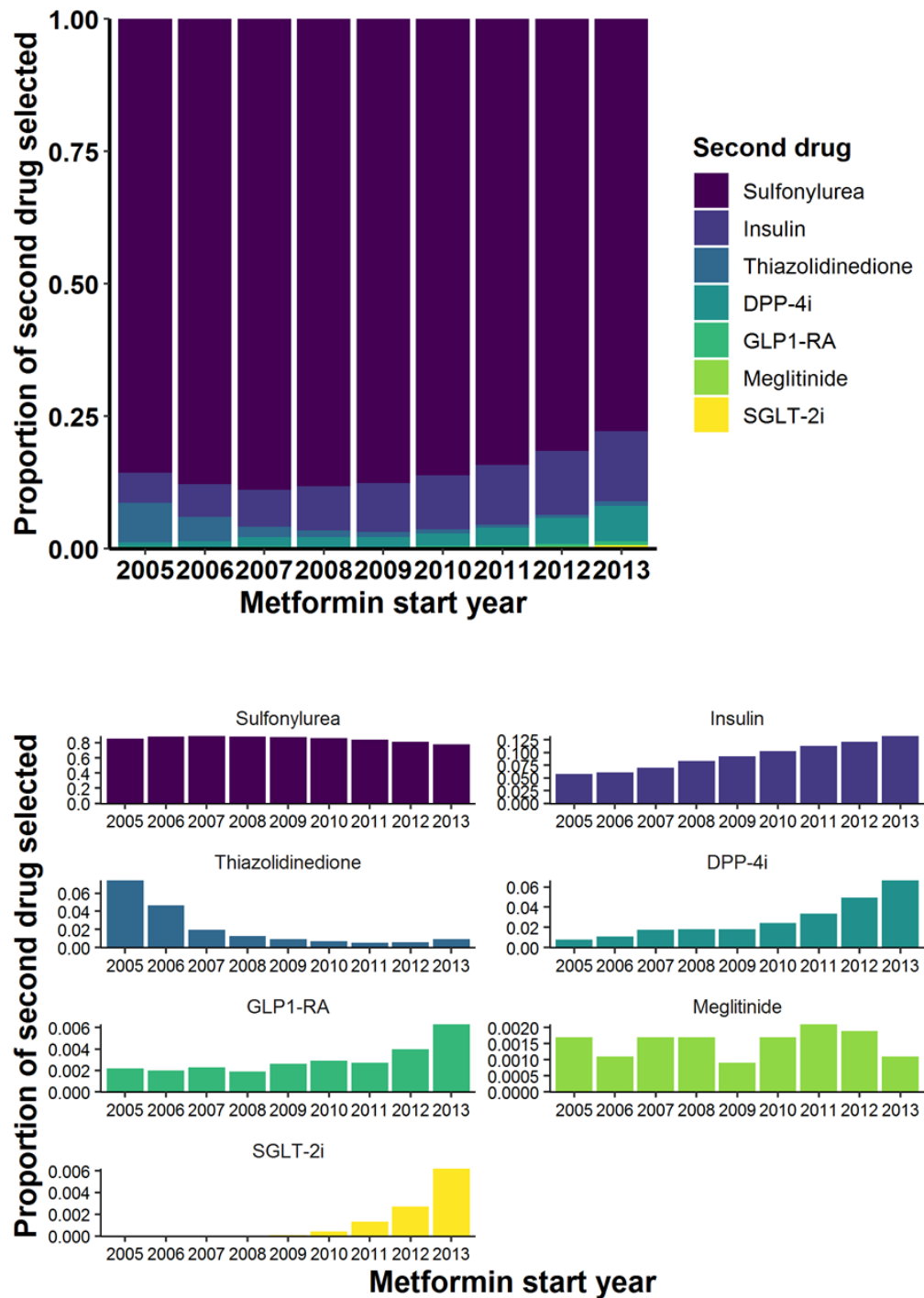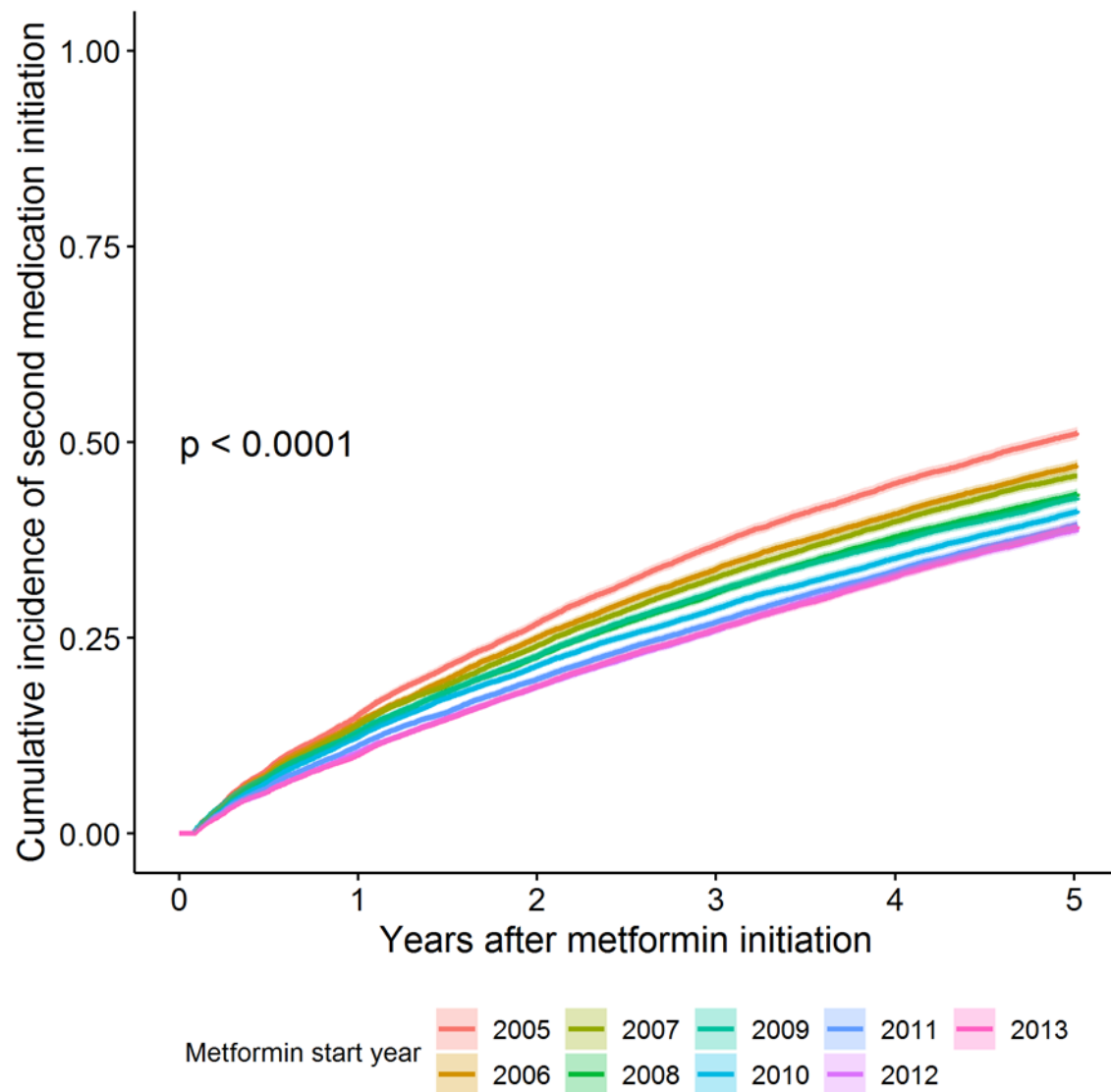

Supplemental Figure 3. Proportion of second-line diabetes medications falling within each of seven medication classes based on year of initial metformin prescription for first-line monotherapy. Second-line medication choices are shown stacked adding up to 100% (**top**) and separately by medication class (**bottom**).

Supplemental Figure 4. Hemoglobin A1c trends at baseline and at initiation of second diabetes medication using narrow baseline definition of occurring between 1 year prior to and 1 month after metformin initiation.

	2005	2006	2007	2008	2009	2010	2011	2012	2013	
HbA1c at baseline (%), mean (SD)	7.32 (1.46)	7.31 (1.39)	7.26 (1.38)	7.23 (1.35)	7.27 (1.34)	7.31 (1.34)	7.37 (1.34)	7.38 (1.36)	7.38 (1.31)	P_{trend} <0.0001
HbA1c at 2nd med initiation (%), mean (SD)	7.76 (1.64)	7.79 (1.64)	7.83 (1.66)	7.95 (1.73)	8.12 (1.76)	8.29 (1.83)	8.38 (1.87)	8.46 (1.90)	8.56 (1.91)	P_{trend} <0.0001

Supplemental Figure 4. Trends in hemoglobin A1c at baseline and at time of initiation of second diabetes medication in the full sample; points and vertical bars represent the mean and standard deviation of hemoglobin A1c for each year. The mean and standard deviation (SD) at baseline and at the initiation of second-line diabetes treatment for each group of patients based on year of metformin monotherapy initiation are shown below the plots. Increasing trend over time in mean HbA1c at baseline and at initiation of second-line treatment were both significant with P_{trend} <0.0001 for both.
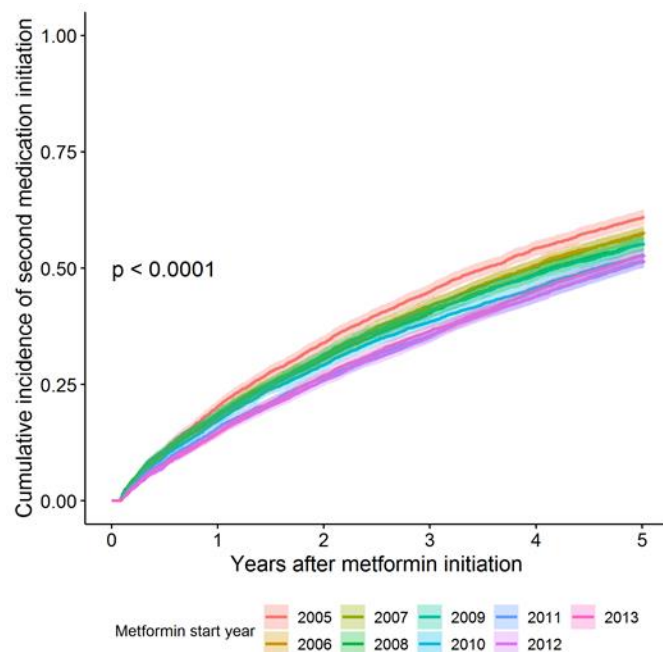
Supplemental Figure 5. Trends in time to second-line diabetes treatment initiation among patients initially treated with metformin monotherapy from 2005-2013.
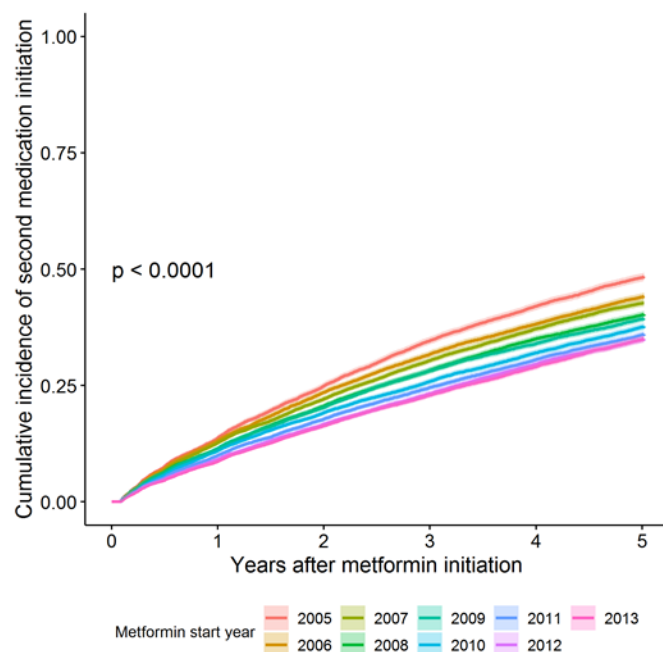

Supplemental Figure 5. Cumulative incidence of initiation of second diabetes medication over five years by year of initial metformin monotherapy for diabetes. Log-rank test p-value for differences in cumulative incidence by initial metformin treatment year is shown.

Supplemental Figure 6. Trends in time to second-line diabetes treatment initiation among patients initially treated with metformin monotherapy from 2005-2013, stratified by baseline age ≤55 years (A) or >55 years (B).

A.

B.

Supplemental Figure 6. Cumulative incidence of initiation of second diabetes medication over five years by year of initial metformin monotherapy for diabetes among those ≤55 years (A) and >55 years (B) of age at the time of initiating metformin. Log-rank test p-value for differences in cumulative incidence by initial metformin treatment year is shown.

Supplemental Figure 7. Trends in HbA1c surveillance frequency among individuals initially treated with metformin monotherapy for diabetes from 2005-2013.

A.

B.
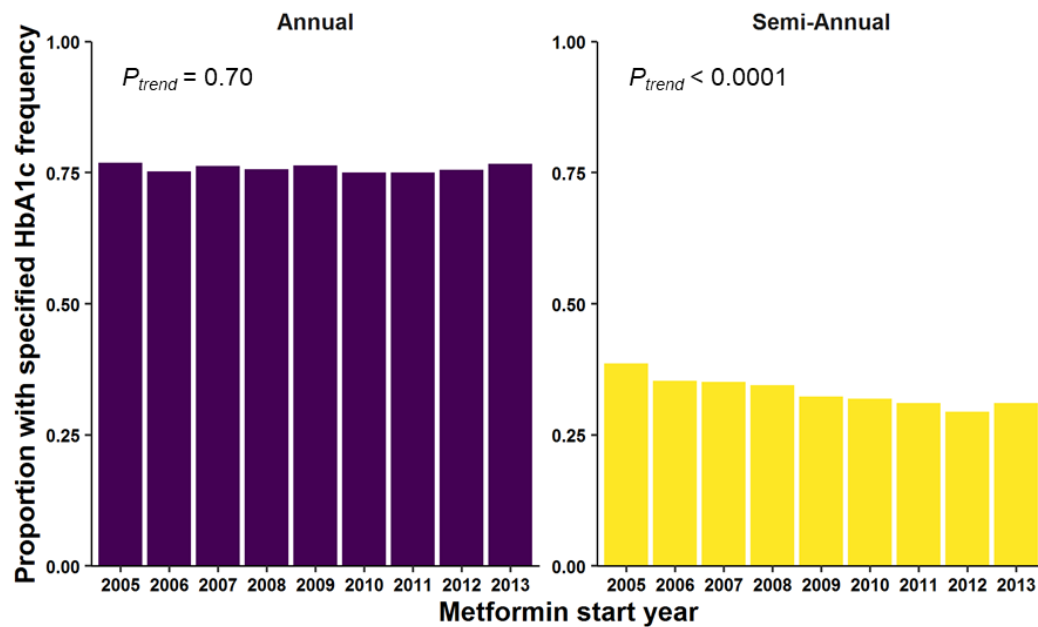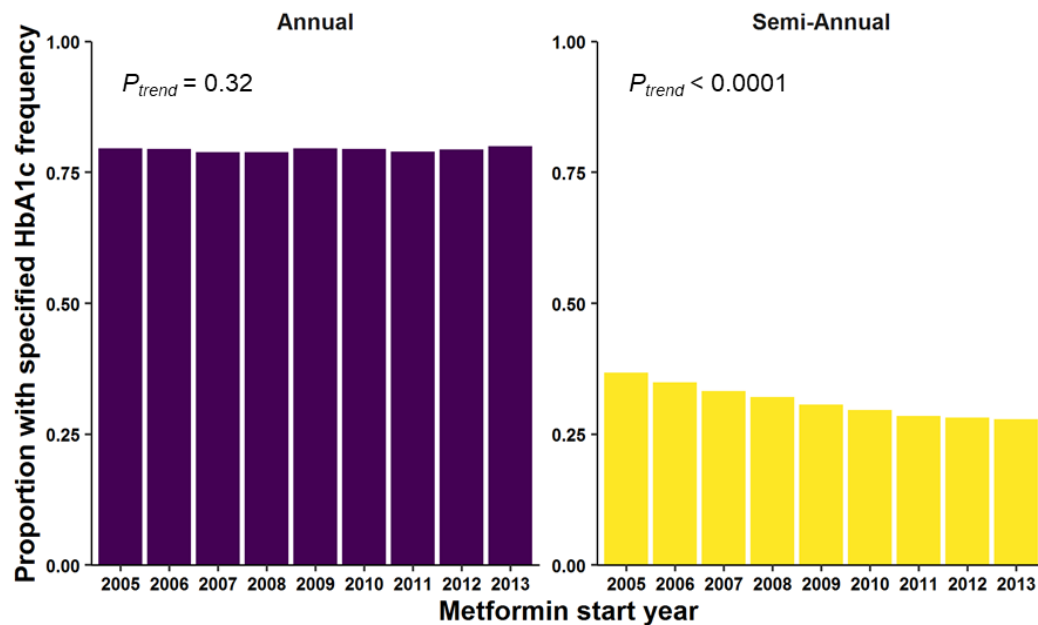
Supplemental Figure 7. Proportions of diabetes patients initially treated with metformin with at least one ("Annual") or two ("Semi-Annual") HbA1c measurements per year between metformin initiation and second-line medication initiation or end of follow-up in those ≤55 years (A) and >55 years old at baseline (B).

STROBE Statement—checklist of items that should be included in reports of observational studies

	Ite m No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	
		Case-control study—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	5-6, 9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	8-9
		(*e̲*) Describe any sensitivity analyses	8-9
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1, Supp Table 2-5
		(b) Indicate number of participants with missing data for each variable of interest	Supp Table 3
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Table 1, Supp Table 5
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10-12
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2, Figure 1-2
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-13, Online Supp

Discussion

Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18
Generalisability	21	Discuss the generalisability (external validity) of the study results	17

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18-19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.