Supplementary Tables S1. Diagnostic ICD-9-CM codes and ATC codes of drugs used in the current study.

Diagnoses	**ICD-9-CM codes**
Uncontrolled diabetes	250.02; 250.12; 250.22; 250.32
Stroke	430-435
Heart failure	428; 398.91; 402.01; 402.11; 402.91; 404.01; 404.03; 404.11; 404.13; 404.91; 404.93
Myocardial infarction	410; 411.0; 412; V45.81; V45.82
Long-term diabetes complications	250.4; 250.5; 250.6; 250.7; 250.8; 250.9
Kidney diseases	582; 585; 586; 588; 583.0; 583.1; 583.4; 583.7; 583.8; 584.6
Diabetic nephropathy	250.40; 250.42
Respiratory diseases	460-519
Cancer	140-239
Retinopathy	362.0; 362.01; 362.02; 362.55; 361; 364.42; 365.63; 369
Depression	296.2; 296.3; 296.82; 296.90; 298.0;
Drugs	**ATC codes**
Antidiabetic drugs	A10B
SGLT2i	A10BK; A10BD15; A10BD16; A10BD20
GLP-1-RA	A10BJ
DPP-4i	A10BH; A10BD07; A10BD08; A10BD10; A10BD11; A10BD13; A10BD18;
Sulfonylureas	A10BB; A10BC; A10BD01; A10BD02; A10BD04; A10BD06
Glinides	A10BX02; A10BX03; A10BX08; A10BD14;
Metformin	A10BA02
Insulin	A10A
Antihypertensive	C02; C03; C07; C08; C09; C10BX03; C10BX09
Antiplatelet	B01AC; C10BX08; C10BX02; C10BX05; C10BX01; N02BA01
Anticoagulant	B01AA; B01AE; B01AF
Antidepressant	N06A
NSAIDs	M01A
Respiratory drugs	R03

Supplementary Table S2. Baseline characteristics of patients treated with second-line glinides and 2nd or 3rd generation sulfonylureas. Unmatched cohort.

	Glinides N = 2,739	Second generation sulfonylureas N = 5,638	Third generation sulfonylureas N = 2,200
Median follow-up (months)	60.7	67.3	71.1
Males	1472 (53.7)	3080 (54.6)	1217 (55.3)
Age categories			
<60	210 (7.7)	1123 (19.9)	450 (20.5)
60–69	522 (19.1)	1583 (28.1)	681 (30.9)
70–79	1029 (37.6)	1982 (35.1)	731 (33.2)
≥80	978 (35.7)	950 (16.9)	338 (15.4)
Duration of treatment with metformin at index date (years)			
<5	765 (27.9)	1668 (29.6)	722 (32.8)
5–9	1230 (44.9)	2675 (47.4)	1029 (46.8)
≥10	744 (27.2)	1295 (23.0)	449 (20.4)
Co-treatments			
Antihypertensive	2474 (90.3)	4577 (81.2)	1748 (79.4)
Antiplatelet	1338 (48.9)	1891 (33.5)	730 (33.2)
Anticoagulant	452 (16.5)	486 (8.6)	150 (6.8)
Antidepressant	568 (20.7)	898 (15.9)	342 (15.5)
Respiratory drugs	771 (28.2)	1300 (23.1)	473 (21.5)
NSAIDs	1017 (37.1)	2159 (38.3)	829 (37.7)
Comorbidities			
Stroke	100 (3.7)	105 (1.9)	48 (2.2)
Heart failure	373 (13.6)	205 (3.6)	46 (2.1)
Myocardial infarction	133 (4.9)	134 (2.4)	41 (1.9)
Renal diseases	222 (8.1)	55 (1.0)	12 (0.6)
Respiratory diseases	415 (15.2)	312 (5.5)	67 (3.1)
Neurological diseases	17 (0.6)	19 (0.3)	8 (0.4)
Retinopathy	1 (0.0)	8 (0.1)	4 (0.2)
Cancer	258 (9.4)	327 (5.8)	99 (4.5)
Depression	14 (0.5)	16 (0.3)	7 (0.3)
Multisource comorbidity score			
Low	951 (34.7)	3393 (60.2)	1378 (62.6)
Intermediate	1333 (48.7)	1872 (33.2)	709 (32.2)
High	455 (16.6)	373 (6.6)	113 (5.1)

Supplementary Table S3. Association between second-line glinides and 2nd or 3rd generation sulfonylureas and primary clinical outcomes.

	Second-line agent		
	Glinides	Second generation sulfonylureas	Third generation sulfonylureas
# patients	2,739	5,638	2,200
MACE [a]			
# (%) of events	1,024 (46.0)	1,582 (30.1)	599 (28.8)
HR (95% CI)	Reference	0.93 (0.86-1.01)	0.91 (0.82-1.01)
MACE new [b]			
# (%) of events	317 (14.3)	557 (10.6)	214 (10.3)
HR (95% CI)	Reference	0.93 (0.80-1.07)	0.89 (0.74-1.06)
All-cause death			
# (%) of events	1,137 (41.5)	1,276 (22.6)	441 (20.1)
HR (95% CI)	Reference	0.91 (0.84-0.99)	0.83 (0.74-0.93)

[a] Myocardial infarction, stroke, heart failure or all-cause deaths

[b] Myocardial infarction, stoke or CV deaths

Supplementary Table S4. Association between second-line therapies and primary clinical outcomes according to the main analysis and selected sensitivity analyses, excluding glinides from the comparison group.

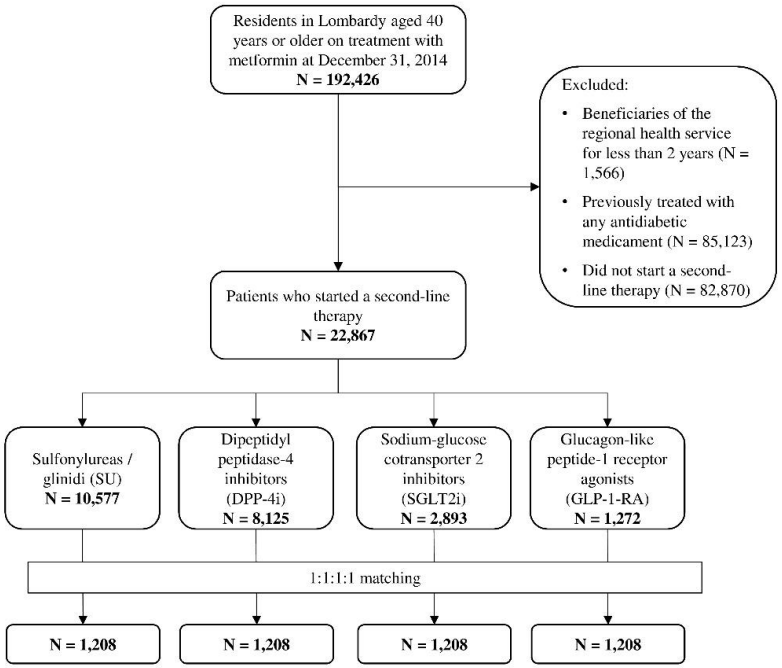
	Second-line agent			
	2nd/3rd generation SU	DPP-4i	SGLT-2i	GLP-1-RA
Main analysis				
# patients	1,001	1,001	1,001	1,001
MACE[a]				
# (%) of events	180 (18.7)	139 (14.7)	124 (12.7)	130 (13.4)
HR (95% CI)	Reference	0.84 (0.65–1.07)	0.75 (0.58–0.96)	0.65 (0.51–0.84)
All-cause death				
# (%) of events	107 (10.7)	83 (8.3)	57 (5.7)	54 (5.4)
HR (95% CI)	Reference	0.78 (0.56–1.07)	0.66 (0.46–0.93)	0.47 (0.33–0.69)
High dimensional propensity score approach				
# patients	1,088	1,088	1,088	1,088
MACE[a]				
# (%) of events	217 (19.9)	200 (18.4)	147 (13.5)	154 (14.2)
HR (95% CI)	Reference	0.99 (0.80–1.21)	0.75 (0.60–0.94)	0.70 (0.56–0.88)
All-cause death				
# (%) of events	120 (11.0)	96 (8.8)	72 (6.6)	57 (5.2)
HR (95% CI)	Reference	0.88 (0.66–1.18)	0.74 (0.54–1.01)	0.46 (0.32–0.65)
Probability-of-censoring weights approach				
# patients	7,838	8,125	2,893	1,272
MACE[a]				
# (%) of events	477 (6.1)	418 (5.1)	109 (3.8)	47 (3.7)
HR (95% CI)	Reference	0.71 (0.57-0.83)	0.67 (0.48-0.94)	0.67 (0.42-1.06)
All-cause death				
# (%) of events	1038 (13.2)	829 (10.2)	97 (3.4)	40 (3.2)
HR (95% CI)	Reference	0.80 (0.70-0.91)	0.65 (0.49-0.86)	0.63 (0.42-0.95)
Different definition of MACE[b]				
# patients	1,001	1,001	1,001	1,001
MACE[b]				
# (%) of events	90 (9.0)	82 (8.2)	71 (7.1)	63 (6.3)
HR (95% CI)	Reference	0.99 (0.72-1.37)	0.88 (0.63-1.22)	0.62 (0.44-0.89)

[a] Composite outcome including myocardial infarction, stroke, heart failure or all-cause deaths

[b] Composite outcome including myocardial infarction, stoke or CV deaths

Supplementary figures.

Supplementary Figure S1. Flow-chart of cohort selection.



Supplementary Figure S2. Forest plot of Hazard Ratio (HR) and corresponding 95% Confidence Interval (CI) showing the effect of newer second-line agents relative to 2nd/3rd generation sulfonylureas and the risk of primary and secondary clinical outcomes estimated from the unmatched cohort.