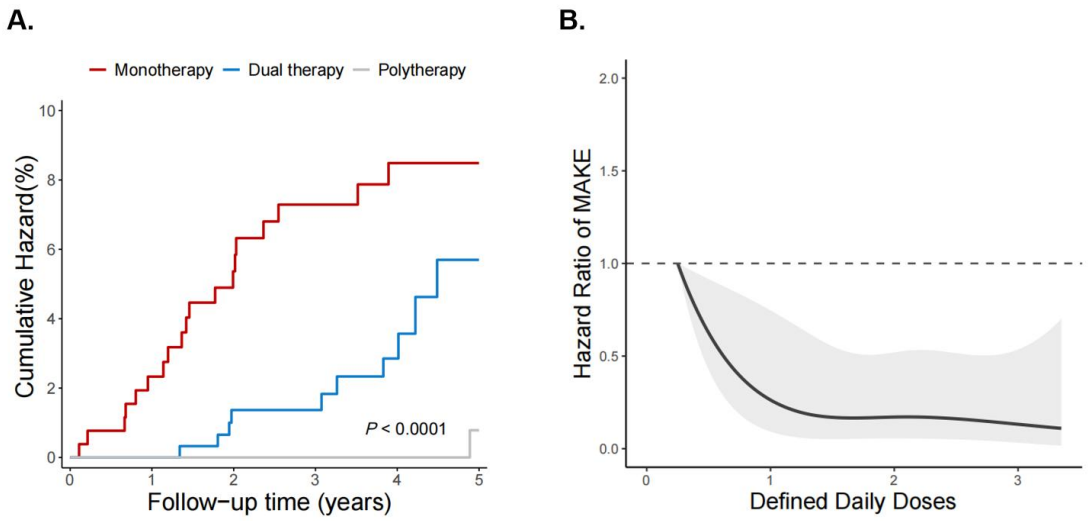


Supplementary Figure 1 Risk of Major Adverse Kidney Events by the Number of Anti-Diabetic Medications and Daily Drug Dose in the Chongqing Diabetes Registry. A: Kaplan-meier curves of major adverse kidney events (MAKE) in CDR. Monotherapy: maintained a single anti-diabetic medication. Dual therapy: maintained 2 anti-diabetic medications. Polytherapy: maintained ≥3 anti-diabetic medications. The MAKE are a composite of end-stage renal disease (defined as estimated glomerular filtration rate ≤15 ml/min/1.73 m^2, initiation of dialysis, or undergoing kidney transplantation) or death attributed to kidney disease; B: Association of daily drug dose with the risk of MAKE using restricted cubic spline (4 knots) for participants in CDR. The analyses are adjusted for use of angiotensin - converting enzyme inhibitor/ angiotensin receptor blocker, mineralocorticoid receptor antagonists, sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists (yes or no) throughout follow-up.

Supplemental Table 1 Protocol for the target trial based on the UK Biobank cohort.

Protocol Components	Target Trial Protocol
Eligibility criteria	Inclusion: 1.age ≥18 years; 2.diagnosis of diabetes; 3.treatment with at least one anti-diabetic agent at baseline; 4.baseline HbA1c ≥ 7%. Exclusion: 1.MAKE at baseline; 2.missing baseline anti-diabetic medication data; 3.loss to follow-up
Treatment strategy	For the target trial comparing combination anti-diabetic therapy with monotherapy. Combination therapy: 1.Initiate use of 2 or ≥3 anti-diabetic medications at the time of enrollment. Monotherapy: 1.Initiate use of one anti-diabetic medication at the time of enrollment.
Treatment assignment	Participants are randomly assigned to either combination anti-diabetic therapy or monotherapy at baseline. Participants will be aware of the assigned treatment strategies.
Follow-up	Follow-up starts at treatment initiation. Participants will be followed until the occurrence of outcome, death, or July 2022, whichever occurs first.

Outcome	MAKE: 1.progression to ESRD, defined as an estimated glomerular filtration rate (eGFR) ≤15 mL/min/1.73 m² (calculated using the CKD-EPI equation); initiation of dialysis (hemodialysis or peritoneal dialysis); or undergoing kidney transplantation; 2.death attributed to kidney disease
Causal contrasts of interest	Intention-to-treat effect.
Analysis plan to estimate causal contrasts of interest	1.Kaplan-Meier estimator to obtain cumulative incidences for each treatment strategy within 15 years of follow-up. 2.Cox proportional hazards analyses to compare rates of time-to-events on daily basis during follow-up time since the baseline. 3.Models are adjusted for confounders at baseline.

Abbreviations: HbA1c, hemoglobin A1c; MAKE: major adverse kidney events.

Supplemental Table 2 Protocol for the target trial based on the Chongqing Diabetes Registry cohort

Protocol Components	Target Trial Protocol
Eligibility criteria	Inclusion: 1.age ≥18 years; 2.diagnosis of diabetes; 3.treatment with at least one anti-diabetic agent at baseline; 4.baseline HbA1c ≥ 7%. Exclusion: 1.MAKE at baseline; 2.missing baseline anti-diabetic medication data; 3.loss to follow-up.
Treatment strategy	For the target trial comparing combination anti-diabetic therapy with monotherapy. Participants will be required to use the assigned medication during follow-up. Combination therapy: 1.Initiate use of 2 or ≥3 anti-diabetic medications at the time of enrollment; 2.Maintained 2 or ≥3 anti-diabetic medication at the time of either an endpoint event or the last follow-up. Monotherapy: 1.Initiate use of one anti-diabetic medication at the time of enrollment; 2.Maintained one anti-diabetic medication at the time of either an endpoint event or the last follow-up.
Treatment assignment	Participants are randomly assigned to either combination anti-diabetic therapy or monotherapy. Participants will be aware of the assigned treatment strategies.

Follow-up	Follow-up starts at treatment initiation. Participants will be followed until the occurrence of outcome, death, or March 2024, whichever occurs first.
Outcome	MAKE: 1.progression to ESRD, defined as an estimated glomerular filtration rate (eGFR) ≤15 mL/min/1.73 m² (calculated using the CKD-EPI equation); initiation of dialysis (hemodialysis or peritoneal dialysis); or undergoing kidney transplantation; 2.death attributed to kidney disease
Causal contrasts of interest	Per-protocol effect of continued use of the assigned medication.
Analysis plan to estimate causal contrasts of interest	1.Kaplan-Meier estimator to obtain cumulative incidences for each treatment strategy within 5 years of follow-up. 2.Cox proportional hazards analyses to compare rates of time-to-events on daily basis during follow-up time since the baseline. 3.Models are adjusted for confounders at baseline and during follow-up.

HbA1c, hemoglobin A1c; MAKE: major adverse kidney events.

Supplementary Table 3 Baseline Anti-diabetic Medication Usage in the UK Biobank

	UK Biobank			
	Monotherapy (n=3,475)		**Combination therapy (n=3,475)**	
	N	%	N	%
Biguanide	1786	51.4%	3334	95.9%
Insulins	1318	37.9%	1385	39.9%
α-Glucosidase inhibitors	0	0.0%	20	0.6%
Sulfonylureas	324	9.3%	2078	59.8%
DPP-4is	/	/	/	/
Glinides	6	0.2%	45	1.3%
Thiazolidinediones	41	1.2%	682	19.6%
SGLT2is	/	/	/	/
GLP-1RAs	/	/	/	/

The data are presented as N and %, derived from the baseline medication information for all participants from UK Biobank. Abbreviations: DPP-4is, dipeptidyl peptidase-4 inhibitors; SGLT2i, sodium-glucose cotransporter-2 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists.

Supplementary Table 4 Baseline Anti-diabetic Medication Usage in the Chongqing Diabetes Registry.

	Chongqing Diabetes Registry			
	Monotherapy (n=261)		**Combination therapy (n=808)**	
	N	%	N	%
Biguanide	55	21.1%	710	87.9%
Insulins	191	73.2%	527	65.2%
α-Glucosidase inhibitors	3	1.1%	246	30.4%
Sulfonylureas	6	2.3%	143	17.7%
DPP-4is	1	0.4%	161	19.9%
Glinides	2	0.8%	104	12.9%
Thiazolidinediones	0	0.0%	14	1.7%
SGLT2is	2	0.8%	210	26.0%
GLP-1RAs	1	0.4%	85	10.5%

The data are presented as N and %, derived from the baseline medication information for all participants from UK Biobank. Abbreviations: DPP-4is, dipeptidyl peptidase-4 inhibitors; SGLT2i, sodium-glucose cotransporter-2 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists.

Supplementary Table 5 Average Dosage of Each Anti-Diabetic Medication Used and Corresponding WHO Defined Daily Doses (DDDs) in Chongqing Diabetes Registry

Category	Generic Names	Average dosage	DDDs
Biguanide	Metformin—mg	1492	2000
Insulins	Insulins—units	30	40
α-Glucosidase inhibitors	Acarbose—mg	174	300
	Voglibose—mg	0.5	0.6
	Miglitol—mg	148	300
Sulfonylureas	Glibenclamide—mg	7	10
	Glipizide—mg	10	10
	Gliquidone—mg	60	60
	Gliclazide—mg	85	60
	Glimepiride—mg	3	2
DPP-4is	Alogliptin—mg	100	25
	Linagliptin—mg	5	5
	Saxagliptin—mg	5	5
	Vildagliptin—mg	67	100
	Sitagliptin—mg	100	100
Glinides	Nateglinide—mg	253	360
	Repaglinide—mg	3	4
Thiazolidinediones	Rosiglitazone—mg	5	6
	Pioglitazone—mg	24	30
SGLT2is	Dapagliflozin—mg	10	10
	Empagliflozin—mg	10	17.5
	Canagliflozin—mg	100	200
GLP-1RAs	Dulaglutide—ug *	1500	160
	Liraglutide—ug	973	1500

Exenatide(Short-acting)—ug	15	15

* These drugs are sustained-release formulations, and the data represent the weekly dosage. Abbreviations: DPP-4is, dipeptidyl peptidase-4 inhibitors; SGLT2i, sodium-glucose cotransporter-2 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists.

Supplementary Table 6 Clinical Characteristics of Participants Receiving Monotherapy or Combination Therapy at Baseline in UK Biobank before Propensity Score Matching

Characteristics	UK Biobank		
	Monotherapy (n = 4,964)	Combination therapy (n = 4,406)	SMD
Age—yr	60.00 (53.00, 65.00)	61.00 (55.00, 65.00)	0.128
Female sex—n (%)	1985 (39.99)	1602 (36.36)	-0.075
Ethnicity (White)	4361 (87.85)	3751 (85.13)	-0.080
Diabetes duration—yr	8.23 (3.81, 18.06)	9.51 (5.76, 14.48)	0.152
Current smoker—n (%)	2577 (51.91)	2443 (55.45)	0.071
Current drinker—n (%)	2595 (52.28)	1937 (43.96)	-0.167
Hypertension—n (%)	3084 (62.13)	3032 (68.82)	0.141
CVD—n (%)	878 (17.69)	884 (20.06)	0.061
CeVD—n (%)	390 (7.86)	384 (8.72)	0.031
BMI—kg/m^2	29.96 (26.56, 34.10)	31.91 (28.53, 36.03)	0.322
HbA1c—%	7.82 (7.35, 8.58)	7.91 (7.40, 8.74)	0.071
Cholesterol—mmol/L	4.42 (3.84, 5.11)	4.19 (3.67, 4.81)	-0.233
Triglycerides—mmol/L	1.81 (1.17, 2.67)	2.00 (1.39, 2.85)	0.121
HDL cholesterol—mmol/L	1.17 (0.98, 1.44)	1.07 (0.92, 1.26)	-0.391
LDL cholesterol—mmol/L	2.59 (2.18, 3.10)	2.49 (2.11, 2.96)	-0.152
Uric acid—umol/L	296.50 (243.98, 360.80)	311.85 (261.92, 368.37)	0.132
eGFR—ml/min/1.73m^2	94.17 (81.75, 101.49)	93.59 (80.03, 100.84)	-0.005
RAS inhibitors—n (%)	881 (17.75)	928 (21.06)	0.084

Dureic—n (%)	924 (18.61)	950 (21.56)	0.074
MRA—n (%)	64 (1.29)	62 (1.41)	0.010

Continuous variables are presented as median (25th and 75th percentiles). Abbreviations: CVD, cardiovascular disease; CeVD, cerebrovascular disease; BMI, body mass index; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; RAS, renin-angiotensin system; MRA, mineralocorticoid receptor antagonist.

Supplementary Table 7 Clinical Characteristics of Participants Receiving Monotherapy or Combination Therapy in Chongqing Diabetes Registry before Propensity Score Matching

Characteristics	Chongqing Diabetes Registry		
	Monotherapy (n = 322)	Combination therapy (n = 1,046)	SMD
Age—yr	56.76 [44.32, 66.05]	59.86 [52.57, 67.25]	0.352
Female sex—n (%)	132 (41.0)	439 (42.0)	0.020
Diabetes duration—yr	8.37 [2.13, 15.09]	10.21 [4.55, 15.96]	0.161
Current smoker—n (%)	129 (40.1)	430 (41.1)	0.021
Current drinker—n (%)	71 (22.0)	237 (22.7)	0.015
Hypertension—n (%)	111 (34.5)	512 (48.9)	0.297
CVD—n (%)	7 (2.2)	42 (4.0)	0.106
CeVD—n (%)	11 (3.4)	33 (3.2)	-0.015
BMI—kg/m^2	22.88 [20.22, 24.97]	24.53 [22.60, 26.73]	0.508
HbA1c—%	9.30 [7.80, 11.28]	9.20 [7.90, 10.70]	0.123
Cholesterol—mmol/L	4.24 [3.48, 5.10]	4.30 [3.58, 5.06]	0.046
Triglycerides—mmol/L	1.27 [0.90, 1.99]	1.54 [1.08, 2.45]	0.282
HDL cholesterol—mmol/L	1.18 [0.94, 1.45]	1.05 [0.88, 1.28]	0.323
LDL cholesterol—mmol/L	2.51 [1.86, 3.18]	2.52 [1.92, 3.26]	0.012
Uric acid—umol/L	305.00 [242.25, 386.50]	313.00 [256.00, 385.00]	0.055
eGFR—ml/min/1.73m^2	83.69 [58.09, 101.98]	88.07 [70.30, 100.22]	0.144
RAS inhibitors—n (%)	50 (15.5)	338 (32.3)	0.401

Dureic—n (%)	17 (5.3)	72 (6.9)	0.067
MRA—n (%)	1 (0.3)	4 (0.4)	0.012

Continuous variables are presented as median (25th and 75th percentiles). Abbreviations: CVD, cardiovascular disease; CeVD, cerebrovascular disease; BMI, body mass index; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; RAS, renin-angiotensin system; MRA, mineralocorticoid receptor antagonist.

Supplementary Table 8 Effects of combination anti-diabetic therapy versus monotherapy on risk of major adverse kidney events.

	HR (95% CI)
UK Biobank: intention-to-treat analysis	
Unadjusted model	0.65(0.46, 0.92)
Adjusting for ACEI/ARB and MRA use at baseline	0.65(0.46, 0.92)
Excluding ACEI/ARB users at baseline	0.59(0.40, 0.87)
Excluding MRA users at baseline	0.65(0.46, 0.93)
Chongqing Diabetes Registry: per-protocol analysis	
Unadjusted model	0.20(0.10, 0.58)
Adjusting for ACEI/ARB, MRA, SGLT2i, and GLP-1RA use at baseline or during follow-up	0.17(0.08, 0.35)
Excluding ACEI/ARB users at baseline or during follow-up	0.18(0.06, 0.58)
Excluding MRA users at baseline or during follow-up	0.20(0.10, 0.40)
Excluding SGLT2i users at baseline or during follow-up	0.21(0.09, 0.53)
Excluding GLP-1RA users at baseline or during follow-up	0.18(0.08, 0.39)

The major adverse kidney events (MAKE) are a composite of end-stage renal disease (defined as estimated glomerular filtration rate ≤15 ml/min/1.73 m2 , initiation of dialysis, or undergoing kidney transplantation) or death attributed to kidney disease. Monotherapy: with a single anti-diabetic medication. Combination therapy: with ≥2 anti-diabetic medications. Abbreviation: ACEI, angiotensin - converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonists; SGLT2i, sodium-glucose cotransporter-2 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists.

Supplementary Table 9 Follow-up HbA1c Level and Self-reported Incidence of Hypoglycemic Events at 2nd and 4th Year Follow-up in Chongqing Diabetes Registry

	Monotherapy	Combination therapy	*P* value
HbA1c level (%)			
Baseline	9.3 [7.8, 11.3]	9.2 [8.0, 10.8]	0.858
2nd year	7.4 [6.5, 8.6]	7.7 [6.9, 8.6]	0.102
4th year	7.7 [6.7, 9.1]	7.7 [7.0, 8.7]	0.340
Hypoglycemic events prevalence (%)			
2nd year	23.7	15.6	0.004
4th year	22.3	14.9	0.018

Self-reported hypoglycemic events include self-monitored fasting blood glucose levels <3.9 mmol/L, or the presence of hypoglycemic symptoms (e.g., palpitations, sweating) without blood glucose measurement, which resolve after food intake. Abbreviation: HbA1c, hemoglobin A1c.