Choice of Glucose-Lowering Drugs as Initial Monotherapy for Type 2 Diabetes Patients with Contraindications or Intolerance to Metformin: A Systematic Review and Meta-Analysis

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27 glucose-lowering drugs from nine drug classes were targeted:

Biguanide	Metformin
SUs	Glyburide, glimepiride, gliclazide, glipizide, and gliquidone
TZDs	Rosiglitazone and pioglitazone
NIDEs	Repaglinide, nateglinide, and mitiglinide
AGIs	Acarbose, voglibose, and miglitol
DPP-4is	Sitagliptin, saxagliptin, vildagliptin, linagliptin, and alogliptin
SGLT2is	Dapagliflozin, empagliflozin, and canagliflozin
INSs	Insulin and insulin analogs
GLP-1RAs	Exenatide, liraglutide, lixisenatide, and beinaglutide

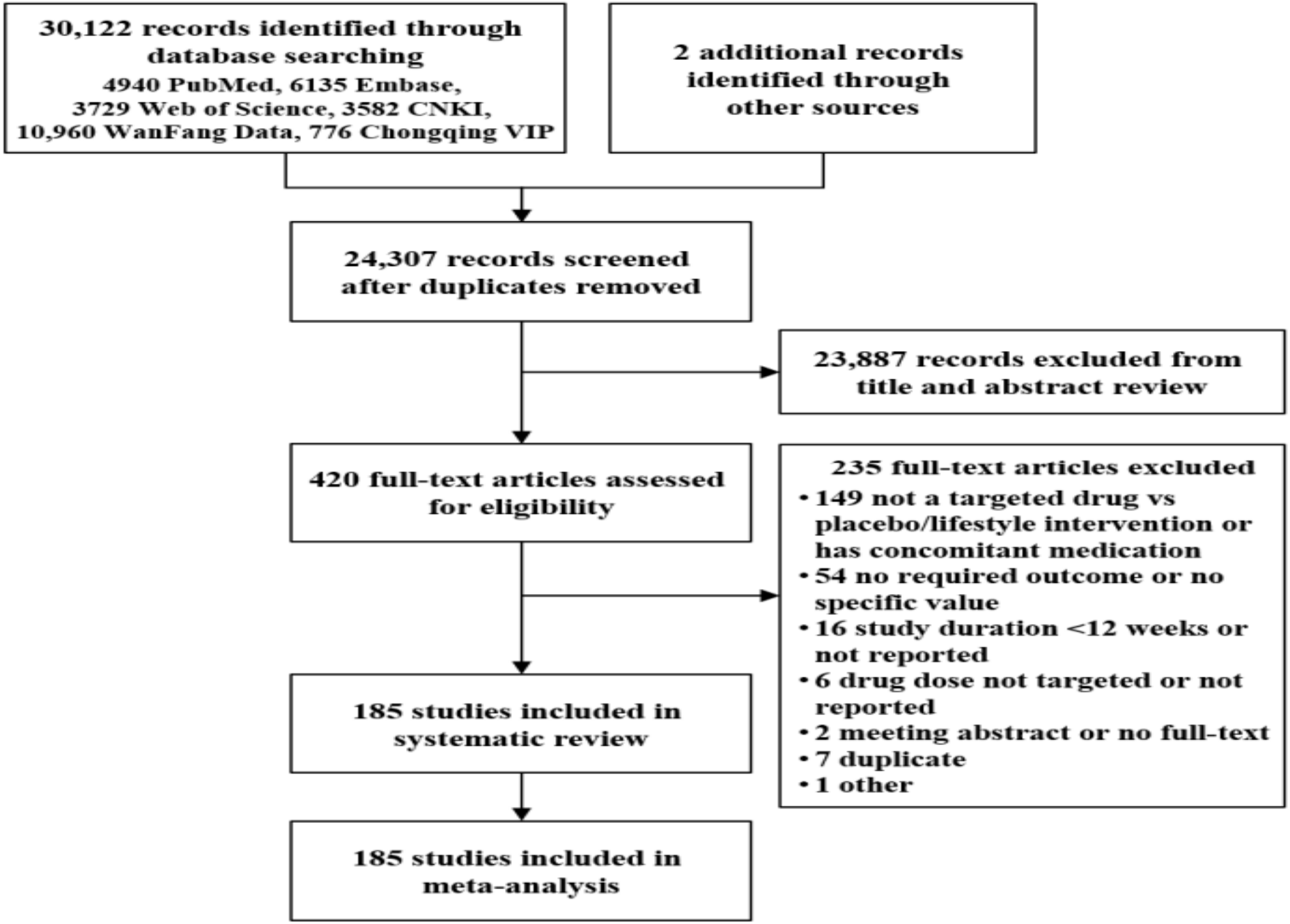

Figure 1. PRISMA flow diagram of study search and selection.

Metformin	−0.96 (−1.16, −0.76) *	−1.65 (−2.02, −1.27) *	−1.28 (−2.26, −0.31) *	−0.30 (−0.47, −0.14) *	0.05 (0.02, 0.09) *	−1.50 (−3.78, 0.79)	1.53 (0.98, 2.40)
SUs	−1.39 (−1.63, −1.16) *	−2.70 (−3.18, −2.23) *	1.22 (0.13, 2.31) *	−0.40 (−1.20, 0.40)	−0.00 (−0.18, 0.18)	1.84 (−4.57, 8.25)	5.44 (2.11, 14.02) *
Glyburide	−1.50 (−2.69, −0.30) *	−2.35 (−3.59, −1.12) *	0.27 (−1.48, 2.03)	−0.80 (−1.94, 0.34)	−0.20 (−0.63, 0.23)	—	—
Glimepiride	−1.36 (−1.57, −1.16) *	−2.41 (−3.09, −1.73) *	1.79 (0.46, 3.12) *	−0.22 (−1.60, 1.17)	0.12 (−0.04, 0.29)	1.84 (−4.57, 8.25)	2.88 (0.45, 18.58)
Gliclazide	−1.40 (−2.70, −0.10) *	−2.22 (−3.47, −0.97) *	—	−0.75 (−1.84, 0.34)	0.07 (−0.08, 0.22)	—	5.00 (0.25, 99.95)
Glipizide	−1.47 (−1.87, −1.06) *	−3.02 (−3.85, −2.20) *	—	0.20 (−3.19, 3.59)	0.41 (−1.64, 2.47)	—	7.11 (2.18, 23.24) *
TZDs	−0.89 (−1.04, −0.73) *	−1.91 (−2.23, −1.60) *	0.63 (0.26, 0.99) *	0.01 (−0.19, 0.22)	0.12 (0.07, 0.17) *	0.78 (−2.37, 3.93)	0.49 (0.23, 1.03)
Rosiglitazone	−0.68 (−0.98, −0.38) *	−1.73 (−2.32, −1.14) *	0.91 (0.48, 1.35) *	0.25 (0.03, 0.46) *	0.06 (0.03, 0.08) *	2.43 (−1.55, 6.42)	0.43 (0.15, 1.26)
Pioglitazone	−1.00 (−1.17, −0.82) *	−2.01 (−2.34, −1.67) *	0.38 (−0.07, 0.82)	−0.09 (−0.32, 0.14)	0.18 (0.09, 0.26) *	−1.79 (−6.33, 2.74)	0.55 (0.20, 1.53)
NIDEs	−0.44 (−0.69, −0.20) *	−0.75 (−1.04, −0.45) *	0.08 (−1.29, 1.44)	0.21 (−0.39, 0.81)	0.08 (−0.21, 0.37)	−5.98 (−12.33, 0.37)	1.37 (0.34, 5.59)
Repaglinide	−0.45 (−0.81, −0.09) *	−0.64 (−1.27, −0.01) *	—	—	—	—	0.97 (0.14, 6.77)
Nateglinide	−0.45 (−0.79, −0.10) *	−0.70 (−1.04, −0.36) *	0.08 (−1.29, 1.44)	0.21 (−0.39, 0.81)	0.08 (−0.21, 0.37)	−5.98 (−12.33, 0.37)	2.00 (0.26, 15.33)
AGIs	−0.62 (−0.79, −0.45) *	−1.19 (−1.73, −0.64) *	−0.49 (−1.26, 0.28)	−0.29 (−0.58, −0.00) *	0.03 (−0.12, 0.17)	−1.40 (−4.71, 1.90)	0.86 (0.51, 1.45)
Acarbose	−0.74 (−0.96, −0.52) *	−1.17 (−1.83, −0.50) *	−0.60 (−1.66, 0.46)	−0.34 (−0.65, −0.03) *	0.07 (−0.11, 0.25)	−1.40 (−4.71, 1.90)	1.19 (0.34, 4.23)
Voglibose	−0.20 (−0.33, −0.07) *	−1.78 (−3.58, 0.02)	0.10 (−0.13, 0.33)	−0.15 (−0.92, 0.62)	−0.17 (−0.48, 0.14)	—	0.93 (0.10, 8.79)
Miglitol	−0.53 (−0.85, −0.21) *	−0.01 (−0.88, 0.86)	—	—	—	—	0.79 (0.44, 1.44)
DPP−4is	−0.63 (−0.68, −0.58) *	−0.94 (−1.03, −0.85) *	0.47 (−0.01, 0.95)	−0.04 (−0.11, 0.02)	0.03 (−0.01, 0.06)	0.02 (−1.10, 1.14)	0.89 (0.67, 1.18)
Sitagliptin	−0.73 (−0.82, −0.65) *	−1.07 (−1.20, −0.95) *	0.10 (−1.24, 1.44)	0.06 (0.01, 0.11) *	0.06 (−0.02, 0.14)	0.18 (−1.27, 1.64)	0.79 (0.52, 1.20)
Saxagliptin	−0.52 (−0.61, −0.44) *	−0.83 (−1.00, −0.67) *	−0.46 (−2.04, 1.12)	—	—	—	1.21 (0.52, 2.81)
Vildagliptin	−0.48 (−0.57, −0.38) *	−0.56 (−0.82, −0.30) *	−0.58 (−2.09, 0.93)	−0.12 (−0.83, 0.59)	—	—	1.07 (0.54, 2.13)
Linagliptin	−0.68 (−0.79, −0.58) *	−0.94 (−1.16, −0.73) *	—	−0.06 (−0.21, 0.09)	0.03 (−0.06, 0.12)	−1.74 (−4.75, 1.26)	0.52 (0.26, 1.01)
Alogliptin	−0.68 (−0.76, −0.61) *	−1.07 (−1.27, −0.86) *	0.81 (0.27, 1.35) *	−0.19 (−0.31, −0.07) *	−0.00 (−0.04, 0.03)	0.59 (−1.59, 2.76)	2.97 (1.00, 8.77) *
SGLT2is	−0.80 (−0.87, −0.72) *	−1.58 (−1.81, −1.36) *	−0.60 (−1.89, 0.69)	0.22 (0.13, 0.31) *	0.09 (0.07, 0.11) *	−4.18 (−4.84, −3.53) *	0.86 (0.55, 1.37)
Dapagliflozin	−0.68 (−0.77, −0.59) *	−1.27 (−1.49, −1.06) *	−0.60 (−1.89, 0.69)	−0.02 (−0.24, 0.20)	0.03 (−0.09, 0.15)	−3.89 (−5.02, −2.75) *	1.29 (0.70, 2.36)
Empagliflozin	−0.79 (−0.86, −0.72) *	−1.84 (−1.97, −1.72) *	—	0.20 (0.06, 0.34) *	0.08 (0.07, 0.10) *	−3.29 (−4.34, −2.25) *	0.31 (0.14, 0.71) *
Canagliflozin	−0.99 (−1.06, −0.92) *	−2.09 (−2.31, −1.87) *	—	0.30 (0.19, 0.40) *	0.10 (0.07, 0.12) *	−5.36 (−6.59, −4.14) *	1.57 (0.79, 3.10)
GLP−1RAs	−0.99 (−1.20, −0.78) *	−1.64 (−2.00, −1.28) *	−1.05 (−1.81, −0.29) *	−0.42 (−0.61, −0.22) *	0.03 (−0.01, 0.06)	−2.98 (−4.67, −1.30) *	1.57 (0.82, 3.02)
Exenatide twice-daily	−0.64 (−0.82, −0.47) *	−1.13 (−1.49, −0.77) *	−1.65 (−2.26, −1.04) *	−0.28 (−0.50, −0.06) *	0.01 (−0.01, 0.03)	−3.19 (−5.47, −0.90) *	3.36 (0.84, 13.52)
Liraglutide	−1.17 (−1.47, −0.87) *	−1.97 (−2.47, −1.47) *	−0.80 (−1.66, 0.07)	−0.56 (−0.78, −0.34) *	0.13 (0.05, 0.21) *	−2.74 (−5.24, −0.25) *	1.37 (0.58, 3.25)
Lixisenatide	−0.60 (−0.83, −0.37) *	−0.97 (−1.47, −0.48) *	—	—	—	—	1.04 (0.25, 4.29)

Glucose-Lowering Drug	Death	Total Vascular Events	Myocardial Infarction	Heart Failure	Stroke	Diabetic Nephropathy	AE-Induced Discontinuations
Metformin	0.88 (0.46, 1.69)	0.91 (0.22, 3.73)	0.98 (0.10, 9.30)	0.98 (0.10, 9.30)	0.98 (0.10, 9.30)	1.59 (0.20, 12.85)	1.03 (0.74, 1.43)
SUs	1.10 (0.27, 4.52)	0.46 (0.03, 7.00)	1.41 (0.06, 33.26)	—	0.16 (0.01, 3.70)	—	2.25 (0.74, 6.81)
Glyburide	1.09 (0.07, 16.30)	—	—	—	—	—	2.24 (0.31, 16.50)
Glimepiride	1.16 (0.15, 9.23)	0.46 (0.03, 7.00)	1.41 (0.06, 33.26)	—	0.16 (0.01, 3.70)	—	0.99 (0.10, 9.40)
Gliclazide	1.00 (0.02, 48.82)	—	—	—	—	—	1.00 (0.02, 48.82)
Glipizide	1.02 (0.02, 50.81)	—	—	—	—	—	4.64 (0.74, 28.95)
TZDs	0.95 (0.48, 1.90)	1.44 (0.38, 5.39)	0.82 (0.13, 5.06)	0.97 (0.19, 4.92)	0.96 (0.13, 7.21)	0.97 (0.02, 48.35)	1.25 (0.81, 1.95)
Rosiglitazone	0.94 (0.29, 3.00)	1.00 (0.02, 46.40)	1.00 (0.02, 46.40)	1.00 (0.02, 46.40)	—	—	0.97 (0.43, 2.23)
Pioglitazone	0.96 (0.41, 2.26)	1.51 (0.37, 6.17)	0.78 (0.10, 6.12)	0.96 (0.16, 5.78)	0.96 (0.13, 7.21)	0.97 (0.02, 48.35)	1.38 (0.82, 2.33)
NIDEs	0.96 (0.20, 4.68)	—	—	—	—	—	0.97 (0.24, 3.81)
Repaglinide	0.97 (0.14, 6.77)	—	—	—	—	—	0.97 (0.14, 6.77)
Nateglinide	0.94 (0.06, 14.46)	—	—	—	—	—	0.96 (0.14, 6.67)
AGIs	1.07 (0.41, 2.78)	1.55 (0.19, 12.51)	1.92 (0.16, 22.74)	—	—	—	2.57 (1.64, 4.03) *
Acarbose	0.97 (0.28, 3.31)	—	—	—	—	—	2.15 (1.23, 3.75) *
Voglibose	0.93 (0.10, 8.78)	0.90 (0.02, 45.04)	—	—	—	—	0.92 (0.19, 4.46)
Miglitol	1.60 (0.20, 12.92)	1.92 (0.16, 22.74)	1.92 (0.16, 22.74)	—	—	—	5.37 (2.11, 13.69) *
DPP-4is	0.89 (0.51, 1.58)	0.82 (0.47, 1.41)	0.47 (0.19, 1.16)	1.00 (0.14, 7.05)	0.99 (0.14, 7.00)	0.98 (0.14, 6.94)	0.92 (0.74, 1.14)
Sitagliptin	0.82 (0.30, 2.20)	0.68 (0.28, 1.66)	0.56 (0.09, 3.53)	1.03 (0.06, 16.28)	0.34 (0.01, 8.36)	—	0.89 (0.62, 1.28)
Saxagliptin	1.44 (0.49, 4.22)	0.71 (0.29, 1.73)	0.33 (0.08, 1.30)	—	—	0.33 (0.01, 8.15)	1.28 (0.68, 2.42)
Vildagliptin	0.48 (0.10, 2.36)	—	—	—	—	—	1.08 (0.73, 1.60)
Linagliptin	0.85 (0.16, 4.50)	0.95 (0.21, 4.25)	0.31 (0.04, 2.52)	—	—	—	0.55 (0.30, 0.99) *
Alogliptin	0.79 (0.18, 3.45)	2.19 (0.39, 12.23)	1.88 (0.16, 22.23)	0.97 (0.06, 15.40)	1.87 (0.16, 22.19)	1.87 (0.16, 22.19)	0.82 (0.42, 1.60)
SGLT2is	0.81 (0.41, 1.60)	1.00 (0.45, 2.21)	0.79 (0.17, 3.64)	1.00 (0.10, 9.50)	0.58 (0.12, 2.88)	1.53 (0.56, 4.18)	0.89 (0.63, 1.24)
Dapagliflozin	1.07 (0.41, 2.80)	1.19 (0.38, 3.68)	—	—	—	1.19 (0.38, 3.68)	1.66 (0.84, 3.27)
Empagliflozin	0.53 (0.15, 1.81)	0.81 (0.21, 3.09)	0.64 (0.08, 5.18)	—	0.34 (0.04, 3.27)	3.95 (0.44, 35.38)	0.56 (0.36, 0.87) *
Canagliflozin	0.77 (0.17, 3.55)	1.00 (0.10, 9.50)	1.00 (0.10, 9.50)	1.00 (0.10, 9.50)	1.00 (0.10, 9.50)	—	1.78 (0.78, 4.07)
GLP-1RAs	0.89 (0.33, 2.43)	0.39 (0.10, 1.57)	0.67 (0.04, 10.13)	0.67 (0.04, 10.13)	0.67 (0.04, 10.13)	0.80 (0.05, 12.41)	1.23 (0.60, 2.54)
Exenatide twice-daily	0.96 (0.14, 6.73)	0.86 (0.02, 40.01)	0.86 (0.02, 40.01)	0.86 (0.02, 40.01)	0.86 (0.02, 40.01)	0.86 (0.02, 40.01)	2.63 (0.49, 14.04)
Liraglutide	0.86 (0.27, 2.79)	0.35 (0.08, 1.55)	0.51 (0.01, 25.66)	0.51 (0.01, 25.66)	0.51 (0.01, 25.66)	0.75 (0.02, 37.38)	0.63 (0.25, 1.61)
Lixisenatide	—	—	—	—	—	—	4.01 (0.85, 18.83)

Table 2. Treatment effects of glucose-lowering drugs compared with each other.

HbA1c, % (Left Lower Half)							**FPG, mmol/L (Right Upper Half)**
Metformin	1.05 (0.45, 1.66) *	0.26 (−0.23, 0.75)	−0.90 (−1.38, −0.42) *	−0.46 (−1.12, 0.20)	−0.71 (−1.10, −0.32) *	−0.07 (−0.51, 0.37)	−0.01 (−0.53, 0.51)
0.43 (0.12, 0.74) *	SUs	−0.79 (−1.36, −0.22) *	−1.95 (−2.51, −1.39) *	−1.51 (−2.23, −0.79) *	−1.76 (−2.24, −1.28) *	−1.12 (−1.65, −0.59) *	−1.06 (−1.66, −0.46) *
−0.07 (−0.32, 0.18)	−0.50 (−0.78, −0.22) *	TZDs	−1.16 (−1.59, −0.73) *	−0.72 (−1.35, −0.09) *	−0.97 (−1.30, −0.64) *	−0.33 (−0.72, 0.06)	−0.27 (−0.75, 0.21)
−0.52 (−0.84, −0.20) *	−0.95 (−1.29, −0.61) *	−0.45 (−0.74, −0.16) *	NIDEs	0.44 (−0.18, 1.06)	0.19 (−0.12, 0.50)	0.83 (0.46, 1.20) *	0.89 (0.43, 1.36) *
−0.34 (−0.60, −0.08) *	−0.77 (−1.06, −0.48) *	−0.27 (−0.50, −0.04) *	0.18 (−0.12, 0.48)	AGIs	−0.25 (−0.80, 0.30)	0.39 (−0.20, 0.98)	0.45 (−0.20, 1.10)
−0.33 (−0.54, −0.12) *	−0.76 (−1.00, −0.52) *	−0.26 (−0.42, −0.10) *	0.19 (−0.06, 0.44)	0.01 (−0.17, 0.19)	DPP−4is	0.64 (0.40, 0.88) *	0.70 (0.33, 1.07) *
−0.16 (−0.37, 0.05)	−0.59 (−0.84, −0.34) *	−0.09 (−0.26, 0.08)	0.36 (0.10, 0.62) *	0.18 (−0.01, 0.37)	0.17 (0.08, 0.26) *	SGLT2is	0.06 (−0.37, 0.49)
0.03 (−0.26, 0.32)	−0.40 (−0.72, −0.09) *	0.10 (−0.16, 0.36)	0.55 (0.23, 0.87) *	0.37 (0.10, 0.64) *	0.36 (0.14, 0.58) *	0.19 (−0.03, 0.41)	GLP−1RAs
BMI, kg/m^2 (Left Lower Half)							**TC, mmol/L (Right Upper Half)**
Metformin	0.10 (−0.72, 0.92)	−0.31 (−0.57, −0.05) *	−0.51 (−1.13, 0.11)	−0.01 (−0.34, 0.32)	−0.26 (−0.44, −0.08) *	−0.52 (−0.71, −0.33) *	0.12 (−0.14, 0.38)
−2.50 (−3.96, −1.04) *	SUs	−0.41 (−1.24, 0.42)	−0.61 (−1.61, 0.39)	−0.11 (−0.96, 0.74)	−0.36 (−1.16, 0.44)	−0.62 (−1.43, 0.19)	0.02 (−0.80, 0.84)
−1.91 (−2.95, −0.87) *	0.59 (−0.56, 1.74)	TZDs	−0.20 (−0.83, 0.43)	0.30 (−0.06, 0.66)	0.05 (−0.17, 0.27)	−0.21 (−0.43, 0.01)	0.43 (0.15, 0.71) *
−1.36 (−3.04, 0.32)	1.14 (−0.61, 2.89)	0.55 (−0.86, 1.96)	NIDEs	0.50 (−0.17, 1.17)	0.25 (−0.35, 0.85)	−0.01 (−0.62, 0.60)	0.63 (−0.00, 1.26)
−0.79 (−2.03, 0.45)	1.71 (0.38, 3.05) *	1.12 (0.27, 1.97) *	0.57 (−1.00, 2.14)	AGIs	−0.25 (−0.55, 0.05)	−0.51 (−0.81, −0.21) *	0.13 (−0.22, 0.48)
−1.75 (−2.84, −0.66) *	0.75 (−0.44, 1.94)	0.16 (−0.44, 0.76)	−0.39 (−1.84, 1.06)	−0.96 (−1.87, −0.05) *	DPP−4is	−0.26 (−0.37, −0.15) *	0.38 (0.17, 0.59) *
−0.68 (−2.30, 0.94)	1.82 (0.13, 3.51) *	1.23 (−0.11, 2.57)	0.68 (−1.20, 2.56)	0.11 (−1.39, 1.61)	1.07 (−0.31, 2.45)	SGLT2is	0.64 (0.43, 0.86) *
−0.23 (−1.47, 1.01)	2.27 (0.94, 3.60) *	1.68 (0.84, 2.52) *	1.13 (−0.43, 2.69)	0.56 (−0.52, 1.64)	1.52 (0.62, 2.42) *	0.45 (−1.05, 1.95)	GLP−1RAs
HDL-C, mmol/L (Left Lower Half)							**SBP, mmHg (Right Upper Half)**
Metformin	−3.34 (−10.15, 3.47)	−2.28 (−6.17, 1.61)	4.48 (−2.27, 11.23)	−0.10 (−4.12, 3.92)	−1.52 (−4.07, 1.03)	2.68 (0.30, 5.06) *	1.48 (−1.36, 4.32)
0.05 (−0.13, 0.23)	SUs	1.06 (−6.08, 8.20)	7.82 (−1.20, 16.84)	3.24 (−3.97, 10.45)	1.82 (−4.69, 8.33)	6.02 (−0.42, 12.46)	4.82 (−1.81, 11.45)
−0.07 (−0.13, −0.01) *	−0.12 (−0.31, 0.07)	TZDs	6.76 (−0.33, 13.85)	2.18 (−2.39, 6.75)	0.76 (−2.58, 4.10)	4.96 (1.74, 8.18) *	3.76 (0.19, 7.33) *
−0.03 (−0.32, 0.26)	−0.08 (−0.42, 0.26)	0.04 (−0.25, 0.33)	NIDEs	−4.58 (−11.74, 2.58)	−6.00 (−12.45, 0.45)	−1.80 (−8.18, 4.58)	−3.00 (−9.57, 3.57)
0.02 (−0.13, 0.17)	−0.03 (−0.26, 0.20)	0.09 (−0.06, 0.24)	0.05 (−0.27, 0.37)	AGIs	−1.42 (−4.91, 2.07)	2.78 (−0.59, 6.15)	1.58 (−2.13, 5.29)
0.02 (−0.03, 0.07)	−0.03 (−0.21, 0.15)	0.09 (0.03, 0.15) *	0.05 (−0.24, 0.34)	0.00 (−0.15, 0.15)	DPP−4is	4.20 (2.90, 5.50) *	3.00 (0.98, 5.02) *
−0.04 (−0.08, 0.00)	−0.09 (−0.27, 0.09)	0.03 (−0.02, 0.08)	−0.01 (−0.30, 0.28)	−0.06 (−0.21, 0.09)	−0.06 (−0.10, −0.02) *	SGLT2is	−1.20 (−3.01, 0.61)
0.02 (−0.03, 0.07)	−0.03 (−0.21, 0.15)	0.09 (0.03, 0.15) *	0.05 (−0.24, 0.34)	0.00 (−0.15, 0.15)	0.00 (−0.05, 0.05)	0.06 (0.02, 0.10) *	GLP-1RAs
Hypoglycemia (Left Lower Half)							**Death (Right Upper Half)**
Metformin	0.80 (0.17, 3.80)	0.93 (0.36, 2.39)	0.92 (0.17, 5.09)	0.83 (0.26, 2.63)	0.99 (0.42, 2.35)	1.09 (0.42, 2.79)	0.99 (0.30, 3.29)
0.28 (0.10, 0.81) *	SUs	1.15 (0.24, 5.55)	1.15 (0.14, 9.57)	1.03 (0.19, 5.67)	1.23 (0.27, 5.65)	1.36 (0.28, 6.51)	1.24 (0.22, 7.01)
3.13 (1.32, 7.42) *	11.08 (3.33, 36.87) *	TZDs	0.99 (0.18, 5.58)	0.89 (0.28, 2.90)	1.07 (0.44, 2.61)	1.18 (0.45, 3.09)	1.07 (0.32, 3.62)
1.12 (0.26, 4.90)	3.97 (0.73, 21.66)	0.36 (0.07, 1.76)	NIDEs	0.90 (0.14, 5.71)	1.08 (0.20, 5.78)	1.19 (0.21, 6.64)	1.08 (0.17, 7.05)
1.79 (0.89, 3.57)	6.33 (2.14, 18.73) *	0.57 (0.23, 1.42)	1.60 (0.36, 7.16)	AGIs	1.20 (0.39, 3.64)	1.32 (0.41, 4.27)	1.20 (0.30, 4.82)
1.73 (1.02, 2.95) *	6.14 (2.28, 16.51) *	0.55 (0.25, 1.22)	1.55 (0.37, 6.49)	0.97 (0.53, 1.76)	DPP-4is	1.10 (0.46, 2.67)	1.01 (0.32, 3.19)
1.78 (0.93, 3.38)	6.30 (2.20, 18.05) *	0.57 (0.24, 1.36)	1.59 (0.36, 6.96)	0.99 (0.49, 2.00)	1.03 (0.60, 1.76)	SGLT2is	0.91 (0.27, 3.07)
0.97 (0.44, 2.15)	3.45 (1.09, 10.91) *	0.31 (0.12, 0.84) *	0.87 (0.19, 4.10)	0.55 (0.24, 1.26)	0.56 (0.28, 1.15)	0.55 (0.25, 1.22)	GLP-1RAs
Total Vascular Events (Left Lower Half)							**AE-Induced Discontinuations (Right Upper Half)**
Metformin	0.46 (0.14, 1.46)	0.82 (0.48, 1.42)	1.07 (0.26, 4.37)	0.40 (0.23, 0.70) *	1.12 (0.76, 1.66)	1.16 (0.73, 1.85)	0.84 (0.38, 1.85)
1.99 (0.09, 42.75)	SUs	1.79 (0.54, 5.91)	2.33 (0.40, 13.59)	0.88 (0.27, 2.90)	2.45 (0.79, 7.58)	2.53 (0.80, 8.06)	1.82 (0.49, 6.85)
0.63 (0.09, 4.37)	0.32 (0.02, 6.59)	TZDs	1.30 (0.31, 5.48)	0.49 (0.26, 0.92) *	1.37 (0.84, 2.23)	1.41 (0.81, 2.46)	1.02 (0.44, 2.37)
—	—	—	NIDEs	0.38 (0.09, 1.59)	1.05 (0.26, 4.22)	1.09 (0.27, 4.46)	0.78 (0.17, 3.69)
0.59 (0.05, 7.30)	0.30 (0.01, 9.16)	0.93 (0.08, 10.98)	—	AGIs	2.80 (1.70, 4.61) *	2.89 (1.65, 5.07) *	2.08 (0.89, 4.88)
1.12 (0.25, 5.08)	0.56 (0.04, 9.07)	1.76 (0.42, 7.38)	—	1.90 (0.22, 16.48)	DPP-4is	1.03 (0.69, 1.54)	0.75 (0.35, 1.58)
0.91 (0.18, 4.61)	0.46 (0.03, 7.86)	1.44 (0.31, 6.74)	—	1.56 (0.17, 14.53)	0.82 (0.31, 2.15)	SGLT2is	0.72 (0.33, 1.60)
2.33 (0.32, 16.87)	1.17 (0.06, 24.97)	3.67 (0.54, 25.02)	—	3.96 (0.32, 48.69)	2.08 (0.47, 9.30)	2.55 (0.51, 12.66)	GLP-1RAs

Treatment estimates are WMD (95% CIs) (or RR (95% CIs)) of the column-defining treatment compared with the row-defining treatment for HbA1c, BMI (or hypoglycemia, total vascular events) (left lower half), and WMD > 0 (or RR > 1) favor the row-defining treatment. Treatment estimates are WMD (95% CIs) of the column-defining treatment compared with the row-defining treatment for HDL-C (left lower half), and WMD > 0 favor the column-