Cost-effectiveness of newer antidiabetic drugs as second-line treatment for type 2 diabetes: A systematic review

Jiejin Zhu [1], Ying Zhou [1], Qingyu Li [1], Gang Wang [1*]

[1] *Department of Clinical Pharmacy, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China*

***Corresponding author:** Wang Gang, BS

Department of Clinical Pharmacy

Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine

No. 261 Huansha Road, Hangzhou, Zhejiang, 310006, China

E-mail: 88485534@163.com

ORCID iDs:

Jiejin Zhu, https://orcid.org/0000-0002-8836-5711

Gang Wang, https://orcid.org/0009-0000-0228-1326

Number of supplementary tables: 5

Supplementary Material

Supplementary Table S1. Search strategy.

	Search strategy	Number of hits
Pubmed		
#1	(Type 2 Diabetes[Title/Abstract]) OR ("Diabetes Mellitus, Type 2"[Mesh])	225,143
#2	second line	101,134
#3	(((Cost-Benefit [Title/Abstract]) OR ("Cost-Benefit Analysis"[Mesh])) OR ((Cost-Effectiveness [Title/Abstract]) OR ("Cost-Effectiveness Analysis"[Mesh]))) OR (Cost Utility [Title/Abstract])	136,235
	#1 AND #2 AND #3	55
Web of Science		
#1	TS=(type 2 diabetes)	249,160
#2	ALL=(second line)	154,330
#3	((TS=(Cost-Benefit)) OR TS=(Cost-Effectiveness)) OR TS=(Cost Utility)	194,930
	#1 AND #2 AND #3	45
Embase		
#1	'type 2 diabetes':ti,ab,kw	249,687
#2	'second line' OR (second AND ('line'/exp OR line))	156,701
#3	'cost benefit':ti,ab,kw OR 'cost effectiveness':ti,ab,kw OR 'cost utility':ti,ab,kw	125,802
	#1 AND #2 AND #3	74
International HTA Database		
	((Diabetes Mellitus, Type 2)[mh] OR (type 2 diabetes)) AND (second line)	12
NIHR HTA journal		
	"type 2 diabetes" and "second line"	22

Search date: April 26, 2023

Supplementary Table S2. Inclusion and exclusion criteria.

	Inclusion criteria	Exclusion criteria
Language	English	
Publication type	original research	editorials, protocol, commentary, reviews, systematic reviews, letters, case study/case series, etc
Publication dates	no limits	
Participants	adults with type 2 diabetes	type 1 diabetes
Intervention	second-line therapy	first-line was not metformin
Outcomes	costs, life years, quality adjusted life years, incremental cost-effective ratios, incremental net monetary benefit	
Study design	full economic evaluations (CEA and CUA)	exclude partial economic evaluations (e.g., only describe burden of illness, cost of illness, cost outcome description)

CEA: cost-effectiveness analysis, *CUA*: cost-utility analysis

Supplementary Table S3. Quality assessment score using CHEERS 2022 checklist

Items	(Ehlers et al., 2022)	(Reifsnider et al., 2022)	(Ehlers et al., 2021)	(Reifsnider et al., 2021)	(Bagepally et al., 2021)	(Ramos et al., 2020)	(Chien et al., 2020)	(Gu et al., 2020)	(Kousoulakou et al., 2017)	(Gordon et al., 2017)	(CADTH, 2017)	(Gu et al., 2016)	(Gordon et al., 2016)	(Tzanetakos et al., 2016)	(Gu et al., 2020)	(Charokopou et al., 2015b)	(Charokopou et al., 2015a)	(Viriato et al., 2014)	(Steen Carlsson and Persson, 2014)	(Kiadaliri et al., 2014)	(Elgart et al., 2013)	(Grzeszczak et al., 2012)	(Granström et al., 2012)	(Erhardt et al., 2012)	(Davies et al., 2012)	(Klarenbach et al., 2011)	(Sinha et al., 2010)	(Schwarz et al., 2008)
1. Title	1	1	1	1	1	1	0.5	0.5	1	0.5	1	1	0.5	1	1	1	1	1	1	1	0.5	1	0.5	1	0.5	0.5	0	1
2. Abstract	1	1	0.5	1	0.5	0.5	0.5	0.5	1	0	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	1	0.5	0.5	1	0.5	0.5	1	0.5
3. Background and objectives	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
4. Health economic analysis plan	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5. Study population	1	1	1	1	0.5	1	1	1	0.5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0.5	0.5	1
6. Setting and location	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	1	1	1	1	0.5	0.5	1	1	1	1	1	0.5	0.5	0.5	0	0.5	0.5	1	0.5	1
7. Comparators	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0.5	1	1	1	1	1	1	1
8. Perspective	0.5	1	1	1	1	1	1	1	1	1	1	0.5	0	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0
9. Time horizon	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0.5	0.5	1	0.5	1	0.5	1	1	0.5
10. Discount rate	1	1	1	1	1	1	1	1	0.5	1	0	1	0.5	1	1	1	1	1	1	0.5	0.5	1	0.5	1	0.5	1	0.5	1
11. Selection of outcomes	1	1	1	1	1	1	1	1	1	1	1	1	0.5	1	1	1	1	1	1	0.5	1	1	1	1	1	0.5	1	1
12. Measurement of outcomes	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
13. Valuation of outcomes	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
14. Measurement and valuation of resources and costs	1	1	1	1	0.5	1	1	1	1	0.5	1	1	1	1	1	1	1	1	1	1	1	0.5	1	1	1	1	1	1
15. Currency, price date, and conversion	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
16. Rationale and description of model	1	0.5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0.5	1
17. Analytics and assumptions	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0.5	1	1	1	0.5	1	1
18. Characterizing heterogeneity	0	0	0	1	0	1	0	0	0	1	1	0	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0	1
19. Characterizing distributional effects	1	1	0	1	0	0	0	0	0	0	1	0.5	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0

20. Characterizing uncertainty	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1
21. Approach to engagement with patients and others affected by the study	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
22. Study parameters	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0.5	0.5	0.5	1	1	0.5	0.5	1	1
23. Summary of main results	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
24. Effect of uncertainty	1	1	0.5	1	0.5	1	1	1	0.5	0.5	1	1	1	1	1	0.5	0.5	0.5	1	0.5	0.5	0.5	1	1	0.5	0.5	0.5	1
25. Effect of engagement with patients and others affected by the study	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
26. Study findings, limitations, generalizability, and current knowledge	0.5	0.5	1	0.5	1	0.5	1	0.5	0.5	1	1	0.5	0.5	0.5	1	0.5	0.5	1	0.5	0.5	0.5	0.5	0.5	0.5	0.5	1	1	1
27. Source of funding	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0
28. Conflicts of interest	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0
Total	**22.5**	**22.5**	**21.5**	**24**	**20.5**	**21.5**	**21.5**	**21**	**21**	**22.5**	**23.5**	**21**	**22**	**21.5**	**22.5**	**21.5**	**21.5**	**22**	**24**	**19**	**19**	**19.5**	**17.5**	**22**	**21**	**19.5**	**18.5**	**20**

Supplementary Table S4. Sensitivity analyses of newer antidiabetic drugs combined with metformin as second-line treatment.

Author, Year	Deterministic sensitivity analyses	Probabilistic sensitivity analyses		
	Key drivers	**Cost-effective**	**Probability**	**WTP**
GLP-1RA vs. SGLT2i				
(Ehlers et al., 2022)	• price of semaglutide (sc) • duration of semaglutide therapy	Empagliflozin	81%	DKK 357,100 (1×GDP per capita)
(Ehlers et al., 2021)	• treatment costs	Empagliflozin	78%	DKK 357,100 (1×GDP per capita)
(Ramos et al., 2020)	• treatment costs	Empagliflozin	95%-97%	GBP 20,000
(Reifsnider et al., 2022)	• drug costs • disutility of injectable treatment • treatment effect on cardiovascular disease	Empagliflozin	100%	USD 50,000
GLP-1RA vs. Others [a]				
(Steen Carlsson and Persson, 2014)	• Earlier initiation of second-line at HbA1c 7%	Liraglutide (vs. Glimepiride) Liraglutide (vs. Sitagliptin)	74% 89%	SEK 500,000
(Davies et al., 2012)	• improvement in HbA1c • improvement in weight • improvement in systolic blood pressure • improvement in weight	Liraglutide 1.2mg / 1.8mg (vs. Sitagliptin) Liraglutide 1.2mg / 1.8mg (vs. Glimepiride)	77% / 85% 82% / 92%	GBP 20,000 GBP 30,000
(Sinha et al., 2010)	• medication costs • side effect duration • side effect associated disutilities	NA	NA	NA
(Kiadaliri et al., 2014)	• BMI related utility • disutility of mild/moderate hypoglycemia • incidence of moderate/major hypoglycemia	GLP-1RA (vs. DPP-4i) GLP-1RA (vs. NPH insulin) DPP-4i (vs. NPH insulin)	74% 100% 98%	SEK 500,000
SGLT2i vs. Others [b]				
(Reifsnider et al., 2021)	• drug costs	Empagliflozin	100%	USD 50,000-150,000
(Charokopou et al., 2015a)	• improvement in weight	Dapagliflozin	85%	GBP 20,000
(Bagepally et al., 2021)	• cost of triple therapy • probabilities of metformin treatment failure	Dapagliflozin	100%	INR 156,798 (1×GDP per capita)

	• probabilities of dual therapy failure			
(Charokopou et al., 2015b)	• improvement in weight • BMI related utility	Dapagliflozin	100%	GBP 20,000
(Tzanetakos et al., 2016)	• BMI related utility	Dapagliflozin (vs. SU)	100%	EUR 34,000
	• improvement in HbA1c	Dapagliflozin (vs. DPP-4i)	79.7%	(2×GDP per capita)
DPP-4i vs. Others [c]				
(Gu et al., 2015)	• BMI related utility • HbA1c baseline	Saxagliptin	74.3%	CNY 43,320 (1×GDP per capita)
(Elgart et al., 2013)	• HbA1c baseline • age baseline • all costs	Saxagliptin	58%	USD 7,626 (1×GDP per capita)
(Granström et al., 2012)	• BMI related utility • HbA1c threshold for third-line therapy	Saxagliptin	72%	SEK 500,000
(Erhardt et al., 2012)	• treatment-induced changes in weight • age baseline • skip first-line	Saxagliptin	Not specified	NA
(Grzeszczak et al., 2012)	• skip first-line • disutilities related to insulin • weight gain • HbA1c baseline	Saxagliptin	74%	USD 36,300 (1×GDP per capita)
(Kousoulakou et al., 2017)	• HbA1c threshold for therapy switch	NA	NA	EUR 13,522 (1×GDP per capita)
(Viriato et al., 2014)	• coefficient of treatment failure • drug costs • drug-specific reduction in HbA1c • discount rates	Vildagliptin	79%	EUR 30,000
(Gordon et al., 2016)	• time horizon	Alogliptin 12.5 / 25 mg	67.6% / 77.1%	GBP 30,000
(Schwarz et al., 2008)	• efficacy of sitagliptin • effect of TZD on systolic blood pressure	NA	NA	EUR 50,000-120,000 (Finland)
(Gu et al., 2016)	• BMI related utility • HbA1c baseline	Saxagliptin	74.7%	CNY 46,629 (1×GDP per capita)

	• HbA1c threshold for therapy switch			
(Gordon et al., 2017)	NA	DPP-4i (vs. SU)	57%	GBP 30,000
		DPP-4i (vs. TZD)	62%	
Multiple antidiabetic drugs				
(CADTH, 2017)	• price of treatments	SU	Not specified	CAD 39,000 to 135,000
		SGLT2i	Not specified	CAD 136,000 to 180,000
		GLP-1RA	Not specified	> CAD 180,000
(Klarenbach et al., 2011)	• price of treatments	SU	100%	CAD 50,000
(Chien et al., 2020)	• baseline HbA1c • baseline age • HbA1c threshold	SGLT2i (DPP-4i as third-line)	70%	NTD 770,770 (1×GDP per capita)
		SGLT2i (SU as third-line)	30%	
(Gu et al., 2020)	• HbA1c threshold for therapy switch • risk equations	Meglitinide (Insulin as third-line)	Not specified	CNY 212,676 (3×GDP per capita)

AGI: α-glucosidase inhibitors, *BMI*: body mass index, *CADTH*: Canadian Agency for Drugs and Technologies in Health, *DPP-4i:* dipeptidyl peptidase-4 inhibitor, *GDP*: gross domestic product, *GLP-1RA*: glucagon-like peptide-1 receptor agonist, *NPH*: neutral protamine Hagedorn, *SGLT2i*: sodium-glucose cotransporter-2 inhibitor, *SU*: sulfonylurea, *TZD*: thiazolidinedione, *WTP*: willing to pay.

[a] GLP-1RA vs. DPP-4i, SU or Insulin.

[b] SGLT2i vs. DPP-4i or SU.

[c] DPP-4i vs. SU, TZD, AGI or Insulin.

Supplementary Table S5. Modelled treatment pathways

Author (Year)	Second-line	Third-line	Fourth-line
GLP-1RA vs. SGLT2i			
(Ehlers et al., 2022)	MET + Semaglutide (sc) or Empagliflozin	(HbA1c > 7.5%) + Glargine 0.7 IU/kg	(HbA1c > 7.5%) MET + Glargine 0.9 IU/kg
(Ehlers et al., 2021)	MET+ Liraglutide or Empagliflozin	(HbA1c > 8%) + Basal bolus	
(Ramos et al., 2020)	MET + Semaglutide (po) or Empagliflozin	(HbA1c > 7.5%) + Glargine 0.7 IU/kg	(HbA1c > 7.5%) Glargine 0.9 IU/kg
(Reifsnider et al., 2022)	MET + Liraglutide or Empagliflozin	(12.6 initiations per 100 person-years) + Empagliflozin or Liraglutide [a]	(3.1 initiations per 100 person-years) + Glargine 80 IU/d [a]
GLP-1RA vs. Others [a]			
(Steen Carlsson and Persson, 2014)	MET + Liraglutide, Glimepiride or Sitagliptin	(HbA1c > 9%) MET + NPH 40 IU/d	
(Davies et al., 2012)	MET + Liraglutide, Glimepiride or Sitagliptin	(Year 6) + Glargine 40 IU/d	
(Sinha et al., 2010)	MET + Glyburide, Exenatide (daily) or Sitagliptin	(treatment failure rate 25% per year) + Rosiglitazone	(treatment failure rate 40% at first year, 50% per year) + NPH insulin 10 IU/d
(Kiadaliri et al., 2014)	MET + GLP-1RA, DPP-4i, or NPH insulin 40 IU/d	(HbA1c > 7.5%) MET + NPH insulin 40 IU/d	(HbA1c > 8%) MET + NPH insulin 60 IU/d
SGLT2i vs. Others [b]			
(Reifsnider et al., 2021)	MET + Empagliflozin or Sitagliptin	(12.6 initiations per 100 person-years) + Sitagliptin or Empagliflozin	(3.1 initiations per 100 person-years) + Glargine 80 IU/d
(Charokopou et al., 2015a)	MET + Dapagliflozin or Sitagliptin	(HbA1c > 8.05%) MET + Basal insulin 40 IU/d	(HbA1c > 8.05%) MET + Basal insulin 60 IU/L
(Bagepally et al., 2021)	MET + Dapagliflozin or SU	(HbA1c > 7%) + Insulin 40 IU/d	
(Charokopou et al., 2015b)	MET + Dapagliflozin or SU	(HbA1c > 7.7%) MET + Basal insulin 40 IU/d	(HbA1c > 7.7%) MET + Basal insulin 60 IU/L
(Tzanetakos et al., 2016)	MET + Dapagliflozin, DPP-4i or SU	(HbA1c > 9%) MET + Basal insulin 40 IU/d	
DPP-4i vs. Others [c]			
(Gu et al., 2015)	MET + Saxagliptin or Glimepiride		
(Elgart et al., 2013)	MET + Saxagliptin or SU	(HbA1c > 7.5%) MET + NPH	
(Granström et al., 2012)	MET + Saxagliptin or Glipizide	(HbA1c > 7.5%) MET + NPH insulin 0.65 IU/kg/d	
(Erhardt et al., 2012)	MET + Saxagliptin or Glipizide	(HbA1c > 7.5%) MET + NPH insulin	
(Grzeszczak et al., 2012)	MET + Saxagliptin or NPH insulin 25 IU/d	(HbA1c > 7%) NPH insulin 40 IU/d	

(Kousoulakou et al., 2017)	MET + Vildagliptin or Glimepiride	(HbA1c > 7%) MET + Basal insulin	(HbA1c > 7%) MET + Intensive insulin
(Viriato et al., 2014)	MET + Vildagliptin	(HbA1c > 7.5%) MET + Multiple-dose insulin	(HbA1c > 7.5%) MET + Multiple-dose insulin
	MET + SU	(HbA1c > 7.5%) MET + Basal-bolus insulin	(HbA1c > 7.5%) MET + Multiple-dose insulin
(Gordon et al., 2016)	MET + Alogliptin or Glipizide	(HbA1c > 7.5%) MET + NPH insulin 47.7 IU/d	
(Schwarz et al., 2008)	MET + Sitagliptin or Rosiglitazone	(HbA1c > 6.5%) MET + Basal insulin	(HbA1c > 6.5%) Multiple-dose insulin
	MET + Sitagliptin or SU	(HbA1c > 6.5%) MET + Basal insulin	(HbA1c > 6.5%) Multiple-dose insulin
	MET + Sitagliptin or SU	(HbA1c > 6.5%) MET + Basal insulin or Rosiglitazone	(HbA1c > 6.5%) Multiple-dose insulin
(Gu et al., 2016)	MET + Saxagliptin or Acarbose	(HbA1c > 7%) MET + Insulin	
(Gordon et al., 2017)	MET + DPP-4i, SU or TZD	(HbA1c > 7.5%) MET + NPH insulin	
Multiple antidiabetic drugs			
(CADTH, 2017)	MET + SU, SGLT2i, GLP-1RA, DPP-4i, Basal insulin or Biphasic insulin		
(Klarenbach et al., 2011)	MET + SU, Meglitinide, AGI, TZD, DPP-4i, Basal insulin or Biphasic insulin		
(Chien et al., 2020)	MET + SGLT2i	(HbA1c > 8%) + SU or DPP-4i	(HbA1c > 8%) MET + Insulin 0.3 IU/kg/d
	MET + DPP-4i	(HbA1c > 8%) + SU or SGLT2i	(HbA1c > 8%) MET + Insulin 0.3 IU/kg/d
	MET + GLP-1RA	(HbA1c > 8%) + SU	(HbA1c > 8%) MET + Insulin 0.3 IU/kg/d
	MET + SU	(HbA1c > 8%) + SU or DPP-4i	(HbA1c > 8%) MET + Insulin 0.3 IU/kg/d
	MET + Insulin 0.2 IU/kg/d	(HbA1c > 8%) + SU	(HbA1c > 8%) MET + Insulin 0.3 IU/kg/d
(Gu et al., 2020)	MET + SU, TZD, AGI, Meglitinide, DPP-4i	(HbA1c > 9%) MET + Insulin or GLP-1RA	

AGI: α-glucosidase inhibitors, *DPP-4i:* dipeptidyl peptidase-4 inhibitor, *CADTH*: Canadian Agency for Drugs and Technologies in Health, *eGFR*: estimated glomerular filtration rate, *GLP-1RA*: glucagon-like peptide-1 receptor agonist, *MET*: metformin, *NPH*: neutral protamine Hagedorn, *SGLT2i*: sodium-glucose cotransporter-2 inhibitor, *SU*: sulfonylurea, *TZD*: thiazolidinedione.

[a] GLP-1RA vs. DPP-4i, SU or Insulin.

[b] SGLT2i vs. DPP-4i or SU.

[c] DPP-4i vs. SU, TZD, AGI or Insulin.