Supplementary Material*

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* This supplementary material was provided by the authors to give readers further details on their article. The material was not copyedited.

Systematic Review Key Question and PICOTS

In adults with type 2 diabetes, what is the effectiveness and harms of DPP-4 inhibitors, GLP-1 agonists, long-acting insulins, SGLT-2 inhibitors, or tirzepatide used either as a monotherapy or in combination with other medications (compared to usual care/placebo or compared with any other approved medication)?

Effectiveness of Newer Therapies for Adults with Type 2 Diabetes	
POPULATION:	Adults with type 2 diabetes
INTERVENTIONS:	DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin), GLP-1 agonists (dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide), SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin), the GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) agonist (tirzepatide), long-acting insulins (degludec, glargine), sulfonylureas (glimepiride, glipizide, glyburide)
COMPARATORS:	Usual therapy/placebo, active comparators (interventions)
MAIN OUTCOMES:	Critical outcomes: all-cause mortality, major adverse cardiac events (MACE), stroke, progression of chronic kidney disease (CKD 3+), myocardial infarction (MI), and serious adverse events (SAEs). Important outcomes: congestive heart failure (CHF) requiring hospitalization and severe hypoglycemia
STUDY DESIGN AND SETTING:	Randomized controlled trials (RCTs) Outpatient

Supplement Table 1. Summary of Findings: DPP-4 Inhibitors, GLP-1 Agonists, Long-acting Insulins, SGLT-2 inhibitors, and Tirzepatide vs. Usual care or Placebo

	Number of RCTs; Total Sample Size Risk Ratio (95% Confidence Interval) Absolute Risk Difference per 1,000 Treated Individuals (95% Confidence Interval) Certainty of Evidence							
	All-Cause Mortality	**MACE**	**MI**	**Stroke**	**CHF Hospitalization**	**CKD 3+**	**SAE**	**Severe Hypoglycemia**
Compared to Usual Care or Placebo								
DPP-4 Inhibitors	K=10; N=47,577 *RR 1.01 (0.94, 1.08) 1 more (4 fewer to 5 more) ⊕⊕⊕	K=5; N=44,595 *RR 1.0 (0.94, 1.06) 0 fewer (6 fewer to 6 more) ⊕⊕⊕	K=2; N=31,015 *RR 0.95 (0.85, 1.06) 2 fewer (6 fewer to 2 more) ⊕⊕⊕	K=1; N=14,523 *RR 0.97 (0.79, 1.19) 1 fewer (5 fewer to 5 more) ⊕⊕⊕	K=3; N = 37,994 *RR 1.06 (0.96, 1.17) 2 more (1 fewer to 6 more) ⊕⊕⊕	K=2; N=23,477 *RR 1.07 (0.95, 1.21) 3 more (2 fewer to 9 more) ⊕⊕⊕	K=9; N=26,256 *RR 0.96 (0.92, 1.01) 8 fewer (15 fewer to 2 more) ⊕⊕⊕	K=9; N= 47,160 *RR 1.14 (1.00, 1.30) 2 more (0 fewer to 5 more) ⊕⊕⊕
Interpretation of relative and absolute risks for DPP-4 inhibitors compared to usual care or placebo**	DPP-4s result in no differences in all-cause mortality	DPP-4s result in no differences in MACE	DPP-4s result in no differences in MI	DPP-4s result in no differences in stroke	DPP-4s result in no differences in hospitalization due to CHF	DPP-4s result in no differences in progression of CKD	DPP-4s result in no differences in SAE	DPP-4s result in no differences in severe hypoglycemia events
	↔	↔	↔	↔	↔	↔	↔	↔
GLP-1 Agonists	K=8; N=48,481 *RR 0.88 (0.83, 0.94) 10 fewer (14 fewer to 5 fewer) ⊕⊕⊕	K=6; N=46,541 *RR 0.91 (0.87, 0.96) 11 fewer (16 fewer to 5 fewer) ⊕⊕⊕	K=5; N=43,244 *RR 0.96 (0.89, 1.04) 3 fewer (7 fewer to 3 more) ⊕⊕⊕	K=5; N=43,244 *RR 0.86 (0.77, 0.95) 5 fewer (7 fewer to 2 fewer) ⊕⊕⊕	K = 4; N = 33,904 *RR 0.95 (0.85, 1.06) 2 fewer (5 fewer to 2 more) ⊕⊕⊕	GLP-1 not in network	K=8; N=36,188 *RR 0.98 (0.95, 1.01) 5 fewer (13 fewer to 3 more) ⊕⊕⊕	K = 8; N = 42,250 *RR 1.02 (0.92, 1.15) 0 fewer (2 fewer to 3 more) ⊕⊕◯
Interpretation of relative and absolute risks for GLP-1 agonists compared to usual care or placebo**	**GLP-1s reduce all-cause mortality by 12% or 10 fewer events per 1,000 treated**	**GLP-1s reduce MACE by 9% or 11 fewer events per 1,000 treated**	GLP-1s result in no differences in MI	**GLP-1s reduce stroke by 14% or 5 fewer events per 1,000 treated**	GLP-1s result in no differences in hospitalization due to CHF	No data	GLP-1s result in no differences in SAE	GLP-1s probably result in no differences in severe hypoglycemia
	↓	↓	↔	↓	↔		↔	↔
Long-acting Insulins	NMA RR 1.23 (0.89, 1.70) ⊕◯◯	NMA RR 1.10 (0.83, 1.46) ⊕◯◯	Long-acting insulin is not in network	Long-acting insulin is not in network	NMA RR 1.01 (0.64, 1.60) ⊕◯◯	Long-acting insulin is not in network	NMA RR 1.17 (0.99, 1.39) ⊕⊕◯	◯◯◯
Interpretation of relative and absolute risks for long-acting insulins compared to usual care or placebo**	Long-acting insulins may result in no differences in all-cause mortality	Long-acting insulins may result in no differences in MACE	No data	No data	Long-acting insulins may result in no differences in hospitalization due to CHF	No data	Long-acting insulins probably result in no differences in SAE	Insufficient evidence
	↔	↔			↔		↔	?
SGLT-2 Inhibitors	K=14; N=47,478 *RR 0.86	K=3; N=19,659 *RR 0.90	K=2; N=15,266 *RR 0.97	K=2; N=15,266 *RR 1.12	K=2; N=11,421 *RR 0.64	K = 4; N=32,713 *RR 0.66	K=14; N=46,096 *RR 0.93	K=9; N=39,902 *RR 0.85

	(0.80, 0.93) 9 fewer (13 fewer to 5 fewer) ⊕⊕⊕	(0.83, 0.98) 12 fewer (21 fewer to 2 fewer) ⊕⊕◯	(0.85, 1.12) 2 fewer (8 fewer to 7 more) ⊕⊕⊕	(0.93, 1.34) 4 more (2 fewer to 10 more) ⊕⊕⊕	(0.54, 0.77) 19 fewer (24 fewer to 12 fewer) ⊕⊕⊕	(0.58, 0.75) 12 fewer (14 fewer to 9 fewer) ⊕⊕⊕	(0.90, 0.95) 23 fewer (33 fewer to 16 fewer) ⊕⊕⊕	(0.74, 0.97) 3 fewer (5 fewer to 1 fewer) ⊕⊕⊕
Interpretation of relative and absolute risks for SGLT-2 inhibitors compared to usual care or placebo**	**SGLT-2s reduce all-cause mortality by 14% or 9 fewer events per 1,000 treated**	**SGLT-2s probably reduce MACE by 10% or 12 fewer events per 1,000 treated**	SGLT-2 results in no differences in MI	SGLT-2 results in no differences in stroke	**SGLT-2s reduce hospitalization due to CHF by 36% or 19 fewer events per 1,000 treated**	**SGLT-2s reduce progression of CKD by 34% or 12 fewer events per 1,000 treated**	**SGLT-2s reduce SAE by 7% or 23 fewer events per 1,000 treated**	**SGLT-2s reduce severe hypoglycemia by 15% or 3 fewer events per 1,000 treated**
	↓	↓	↔	↔	↓	↓	↓	↓
Tirzepatide	NMA RR 0.98 (0.56, 1.73) ⊕◯◯	◯◯◯	Tirzepatide is not in network	Tirzepatide is not in network	Tirzepatide is not in network	Tirzepatide not in network	K=3; N=1,069 *RR 0.79 (0.51, 1.22) 17 fewer (39 fewer to 17 more) ⊕⊕⊕	K=3; N=1,373 *RR 1.32 (0.78, 2.22) 15 more (10 fewer to 55 more) ⊕⊕◯
Interpretation of relative and absolute risks for tirzepatide compared to usual care or placebo**	Tirzepatide may result in no differences in all-cause mortality	Insufficient evidence	No data	No data	No data	No data	Tirzepatide results in no differences in SAE	Tirzepatide probably results in no differences in severe hypoglycemia
	↔	?					↔	↔

Color key: Favors intervention; Favors comparator; No difference (not colored)

Favors intervention or favors comparator indicates a statistically significant difference between the intervention and comparison or a meaningful difference in effect size (i.e., >25% increase or decrease) with 95% CIs not crossing both lower (0.75) and upper bound (1.25) intervals.

Bold interpretation text indicates statistically significant findings.

Serious adverse events were defined by investigators, varied, and not always fully reported. In general, they included events considered fatal or life threatening, and incorporated events (e.g., stroke, MI) that could also be a clinical benefit (through a reduction) with type 2 diabetes treatment (1). Long-acting insulins and sulfonylureas directly cause hypoglycemia and were used either as a direct comparator or within usual care, which may distort findings.

GRADE certainty of evidence: Insufficient ◯◯◯; Low ⊕◯◯; Moderate ⊕⊕◯; High ⊕⊕⊕

*Estimate from direct comparison because it has a higher certainty of evidence than the network estimate

** Interpretation of findings was done by the Clinical Guidelines Committee; Statistics and GRADE ratings are from the ACP-funded evidence review (1)

Summary of CGC Judgments - Usual Care or Placebo

	DPP-4 INHIBITORS VS. USUAL CARE/PLACEBO	GLP-1 AGONISTS VS. USUAL CARE/PLACEBO	LONG-ACTING INSULINS VS. USUAL CARE/PLACEBO	SGLT-2 INHIBITORS VS. USUAL CARE/PLACEBO	TIRZEPATIDE VS. USUAL CARE/PLACEBO
DESIRABLE EFFECTS	No clinically meaningful differences	Medium	No clinically meaningful differences	Medium	No clinically meaningful differences
UNDESIRABLE EFFECTS	No clinically meaningful differences	No clinically meaningful differences	No clinically meaningful differences	No clinically meaningful differences	No clinically meaningful differences
CERTAINTY OF EVIDENCE	High	High	Low	High	Insufficient
VALUES	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability
BALANCE OF EFFECTS	Does not favor either the intervention or the comparison	Favors the intervention	May not favor either the intervention or the comparison	Favors the intervention	Don't know
RESOURCES REQUIRED	Large differences in costs	Large differences in costs	Large differences in costs	Large differences in costs	Don't know
COST EFFECTIVENESS	No studies	Intermediate-value intervention	No studies	Intermediate-value intervention	Uncertain

Supplement Table 2. Summary of Findings: DPP-4 Inhibitors vs. Other Medications

	Number of RCTs; Total Sample Size Risk Ratio (95% Confidence Interval) Absolute Risk Difference per 1,000 Treated Individuals (95% Confidence Interval) Certainty of Evidence							
	All-Cause Mortality	**MACE**	**MI**	**Stroke**	**CHF Hospitalization**	**CKD 3+**	**SAE**	**Severe Hypoglycemia**
DPP-4 Inhibitors (Head-to-Head)								
DPP-4 Inhibitors vs. GLP-1 Agonists	K = 4; N=4,612 *RR 1.64 (1.05, 2.56) 7 more (1 more to 14 more) ⊕⊕◯	K = 1; N = 2,515 *RR 1.42 (0.99, 2.04) 16 more (0 fewer to 40 more) ⊕⊕⊕	NMA RR 0.98 (0.86, 1.13) ⊕⊕◯	NMA RR 1.14 (0.90, 1.43) ⊕⊕◯	K = 1; N = 2,515 *RR 2.12 (1.13, 3.98) 13 more (1 more to 33 more) ⊕⊕◯	GLP-1 is not in network	K = 5; N=5,168 *RR 1.07 (0.89, 1.29) 6 more (10 fewer to 26 more) ⊕⊕⊕	K = 4; N = 6,724 *RR 1.25 (0.91, 1.73) 7 more (2 fewer to 20 more) ⊕⊕⊕
Interpretation of relative and absolute risks for DPP-4 inhibitors compared to GLP-1 agonists**	**DPP-4s probably increase all-cause mortality by 64% or 7 more events per 1,000 treated**	DPP-4s increase MACE by 42% or 16 more events per 1,000 treated	DPP-4s probably result in no differences in MI	DPP-4s probably result in no differences in stroke	**DPP-4s probably increase hospitalization due to CHF by 112% or 13 more events per 1,000 treated**	No data	DPP-4s result in no differences in SAEs	DPP-4s result in no differences in severe hypoglycemia
	↑	↑	↔	↔	↑		↔	↔
DPP-4 Inhibitors vs. Long-acting insulins	K = 1; N = 2,531 *RR 0.97 (0.64, 1.48) 1 fewer (12 fewer to 16 more) ⊕⊕⊕	K = 1; N = 2,521 *RR 1.06 (0.76, 1.47) 3 more (12 fewer to 24 more) ⊕⊕⊕	Long-acting insulins are not in network	Long-acting insulins are not in network	K=1; n = 2,521 *RR 1.15 (0.68, 1.93) 3 more (7 fewer to 19 more) ⊕⊕⊕	Long-acting insulins are not in network	NMA RR 0.82 (0.68, 0.97) ⊕◯◯	K = 1; N=2,531 *RR 0.56 (0.25, 1.26) 6 fewer (10 fewer to 3 more) ⊕⊕◯
Interpretation of relative and absolute risks for DPP-4 inhibitors compared to long-acting insulins**	DPP-4s result in no differences in all-cause mortality	DPP-4s result in no differences in MACE	No data	No data	DPP-4s result in no differences in hospitalization due to CHF	No data	**DPP-4s may reduce SAE by 18%**	DPP-4s probably result in no differences in severe hypoglycemia
	↔	↔			↔		↓	↔
DPP-4 Inhibitors vs. SGLT-2 Inhibitors	K = 5; N=3,878 *RR 1.20 (0.32, 4.48) 0 fewer (2 fewer to 8 more) ⊕◯◯	NMA RR 1.13 (1.03, 1.25) ⊕⊕◯	NMA RR 0.98 (0.82, 1.17) ⊕⊕◯	NMA RR 0.87 (0.66, 1.15) ⊕⊕◯	NMA RR 1.68 (1.36, 2.07) ⊕◯◯	NMA RR 1.62 (1.36, 1.94) ⊕⊕◯	K = 4; N =3,455 *RR 0.99 (0.75, 1.31) 1 fewer (14 fewer to 17 more) ⊕⊕⊕	K = 4; N = 3,105 *RR 0.78 (0.10, 5.99) 0 fewer (2 fewer to 10 more) ⊕◯◯
Interpretation of relative and absolute risks for DPP-4 inhibitors compared to SGLT-2 inhibitors**	DPP-4s may result in no differences in all-cause mortality	**DPP-4s probably increase MACE by 13%**	DPP-4s probably result- in no differences in MI	DPP-4s probably result- in no differences in stroke	**DPP-4s may increase hospitalization due to CHF by 68%**	**DPP-4s probably increase progression of CKD by 62%**	DPP-4s result in no differences in SAE	DPP-4s may result in no differences in severe hypoglycemia
	↔	↑	↔	↔	↑	↑	↔	↔

DPP-4 Inhibitors vs. Sulfonylurea	K = 10; N = 22,352 *RR 0.90 (0.79, 1.03) 4 fewer (8 fewer to 1 more) ⊕⊕⊕	K = 4; N = 12,715 *RR 0.96 (0.85, 1.09) 3 fewer (12 fewer to 7 more) ⊕⊕⊕	K=1; N=6,033 *RR 1.03 (0.83, 1.28) 1 more (8 fewer to 14 more) ⊕⊕⊕	K=1; N=6,033 *RR 0.86 (0.67, 1.12) 6 fewer (13 fewer to 5 more) ⊕⊕⊕	K = 2; N = 8,544 *RR 1.16 (0.91, 1.47) 5 more (3 fewer to 13 more) ⊕⊕⊕	Sulfonylurea is not in network	K=10; N=20,439 *RR 0.95 (0.91, 0.99) 12 fewer (21 fewer to 2 fewer) ⊕⊕◯	K = 8; N = 18,081 *RR 0.14 (0.11, 0.19) 44 fewer (46 fewer to 42 fewer) ⊕⊕⊕
Interpretation of relative and absolute risks for DPP-4 inhibitors compared to sulfonylurea**	DPP-4s result in no differences in all-cause mortality	DPP-4s result in no differences in MACE	DPP-4s result in no differences in MI	DPP-4s result in no differences in stroke	DPP-4s result in no differences in hospitalization due to CHF	No data	**DPP-4s probably reduce SAE by 5% or 12 fewer events per 1,000 treated**	**DPP-4s reduce severe hypoglycemia by 86% or 44 fewer events per 1,000 treated**
	↔	↔	↔	↔	↔		↓	↓
DPP-4 Inhibitors vs. Tirzepatide	NMA RR 1.04 (0.59, 1.83) ⊕◯◯	NMA RR 1.21 (0.76, 1.92) ⊕◯◯	Tirzepatide is not in network	Tirzepatide is not in network	Tirzepatide is not in network	Tirzepatide is not in network	NMA RR 0.99 (0.80, 1.22) ⊕⊕◯	 ◯◯◯
Interpretation of relative and absolute risks for DPP-4 inhibitors compared to tirzepatide**	DPP-4s may result in no differences in all-cause mortality	DPP-4s may result in no differences in MACE	No data	No data	No data	No data	DPP-4s probably result in no differences in SAE	Insufficient evidence
	↔	↔					↔	?

Color key: Favors intervention; Favors comparator; No difference (not colored)

Favors intervention or favors comparator indicates a statistically significant difference between the intervention and comparison or a meaningful difference in effect size (i.e., >25% increase or decrease) with 95% CIs not crossing both lower (0.75) and upper bound (1.25) intervals.

Bold interpretation text indicates statistically significant findings.

Serious adverse events were defined by investigators, varied, and not always fully reported. In general, they included events considered fatal or life threatening, and incorporated events (e.g., stroke, MI) that could also be a clinical benefit (through a reduction) with type 2 diabetes treatment (1). Long-acting insulins and sulfonylureas directly cause hypoglycemia and were used either as a direct comparator or within usual care, which may distort findings.

GRADE certainty of evidence: Insufficient ◯◯◯; Low ⊕◯◯; Moderate ⊕⊕◯; High ⊕⊕⊕

*Estimate from direct comparison because it has a higher certainty of evidence than the network estimate

** Interpretation of findings was done by the Clinical Guidelines Committee; Statistics and GRADE ratings are from the ACP-funded evidence review (1)

Summary of CGC Judgments - DPP-4 Inhibitors

	DPP-4 INHIBITORS VS. GLP-1 AGONISTS	DPP-4 INHIBITORS VS. LONG-ACTING INSULINS	DPP-4 INHIBITORS VS. SGLT-2 INHIBITORS	DPP-4 INHIBITORS VS. SULFONYLUREA	DPP-4 INHIBITORS VS. TIRZEPATIDE
DESIRABLE EFFECTS	No clinically meaningful differences	No clinically meaningful differences	No clinically meaningful differences	Small	No clinically meaningful differences
UNDESIRABLE EFFECTS	Medium	No clinically meaningful differences	Medium	No clinically meaningful differences	No clinically meaningful differences
CERTAINTY OF EVIDENCE	Moderate	Low	Low	Moderate	Low
VALUES	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability
BALANCE OF EFFECTS	Probably favors the comparison	May not favor either the intervention or the comparison	May favor the comparison	Probably favors the intervention	May not favor either the intervention or the comparison
RESOURCES REQUIRED	Modest differences in savings	Negligible differences in costs and savings	Negligible differences in costs and savings	Large differences in costs	Don't know
COST EFFECTIVENESS	No studies	No studies	No studies	Low-value intervention	No studies

Supplement Table 3. Summary of Findings: GLP-1 Agonists vs. Other Medications

	Number of RCTs; Total Sample Size Risk Ratio (95% Confidence Interval) Absolute Risk Difference per 1,000 Treated Individuals (95% Confidence Interval) Certainty of Evidence							
	All-Cause Mortality	**MACE**	**MI**	**Stroke**	**CHF Hospitalization**	**CKD 3+**	**SAE**	**Severe Hypoglycemia**
GLP-1 Agonists (Head-to-Head)								
GLP-1 Agonists vs. DPP-4 Inhibitors	K = 4; N=4,612 *RR 0.61 (0.39, 0.95) 9 fewer (14 fewer to 1 fewer) ⊕⊕◯	K = 1; N = 2,515 *RR 0.70 (0.49, 1.01) 16 fewer (28 fewer to 1 more) ⊕⊕⊕	NMA RR 1.02 (0.88, 1.16) ⊕⊕◯	NMA RR 0.88 (0.70, 1.11) ⊕⊕◯	K = 1; N = 2,515 *RR 0.47 (0.25, 0.88) 13 fewer (18 fewer to 3 fewer) ⊕⊕◯	GLP-1 not in network	K = 5; N = 5,168 *RR 0.94 (0.78, 1. 13) 5 fewer (20 fewer to 12 more) ⊕⊕⊕	K = 4; N = 6,724 *RR 0.81 (0.59, 1.11) 4 fewer (9 fewer to 2 more) ⊕⊕⊕
Interpretation of relative and absolute risks for GLP-1 Agonists compared to DPP-4 Inhibitors**	**GLP-1s probably reduce all-cause mortality by 39% or 9 fewer events per 1,000 treated**	GLP-1s reduce MACE by 30% or 16 fewer events per 1,000 treated	GLP-1s probably result in no differences in MI	GLP-1s probably result in no differences in stroke	**GLP-1s probably reduce hospitalization due to CHF by 53% or 13 fewer events per 1,000 treated**	No data	GLP-1s result in no differences in SAEs	GLP-1s result in no differences in severe hypoglycemia
	↓	↓	↔	↔	↓		↔	↔
GLP-1 Agonists vs. Long-acting insulins	K = 4; N = 4,792 *RR 0.62 (0.41, 0.93) 10 fewer (16 fewer to 2 fewer) ⊕⊕◯	K = 1; N = 2,508 *RR 0.74 (0.52, 1.07) 13 fewer (25 fewer to 4 more) ⊕⊕⊕	Long-acting insulins are not in network	Long-acting insulins are not in network	K = 1; N = 2,508 *RR 0.54 (0.28, 1.03) 10 fewer (15 fewer to 1 more) ⊕⊕◯	GLP-1 and long-acting insulins are not in network	K=5; N=3,579 *RR 0.86 (0.72, 1.04) 16 fewer (33 fewer to 5 more) ⊕◯◯	K = 6; N = 6,104 *RR 0.23 (0.16, 0.33) 38 fewer (42 fewer to 33 fewer) ⊕⊕◯
Interpretation of relative and absolute risks for GLP-1 Agonists compared to long-acting insulins**	**GLP-1s probably reduce all-cause mortality by 38% or 10 fewer events per 1,000 treated**	GLP-1s reduce MACE by 26% or 13 fewer events per 1000 treated	No data	No data	GLP-1s probably reduce hospitalization due to CHF by 46% or 10 fewer events per 1,000 treated	No data	GLP-1s may result in no differences in SAEs	**GLP-1s probably reduce severe hypoglycemia by 77% or 38 fewer events per 1000 treated**
	↓	↓			↓		↔	↓
GLP-1 Agonists vs. SGLT-2 Inhibitors	NMA RR 1.02 (0.93, 1.12) ⊕⊕◯	NMA RR 1.01 (0.92, 1.11) ⊕⊕◯	NMA RR 0.99 (0.85, 1.16) ⊕⊕◯	NMA RR 0.77 (0.62, 0.95) ⊕⊕◯	NMA RR 1.44 (1.16, 1.78) ⊕⊕◯	GLP-1s are not in network	K = 2; N = 1,249 *RR 0.93 (0.60, 1.45) 4 fewer (25 fewer to 28 more) ⊕⊕◯	K = 3; N = 2,068 *RR 1.00 (0.47, 2.14) 0 fewer (7 fewer to 14 more) ⊕⊕◯
Interpretation of relative and absolute risks for	GLP-1s probably result in no differences in all-cause mortality	GLP-1s probably result in no differences in MACE	GLP-1s probably result in no differences in MI	**GLP-1s probably reduce stroke by 23%**	**GLP-1s probably increase hospitalization due to CHF by 44%**	No data	GLP-1s probably result in no differences in SAEs	GLP-1s probably result in no differences in

GLP-1 Agonists compared to SGLT-2 Inhibitors**								severe hypoglycemia
	↔	↔	↔	↓	↑		↔	↔
GLP-1 Agonists vs. Sulfonylurea	K = 3; N = 4,281 *RR 0.67 (0.44, 1.04) 8 fewer (13 fewer to 10 more) ⊕⊕⊕	K = 1; N =2,498 *RR 0.81 (0.56, 1.18) 9 fewer (21 fewer to 9 more) ⊕⊕⊕	◯◯◯	◯◯◯	K = 1; N = 2,498 *RR 0.47 (0.25, 0.87) 13 fewer (18 fewer to 3 fewer) ⊕⊕◯	GLP-1s and Sulfonylurea are not in network	K = 2; N = 1,765 *RR 1.08 (0.83, 1.41) 9 more (20 fewer to 48 more) ⊕⊕◯	K = 3; N =4,281 *RR 0.49 (0.26, 0.92) 7 fewer (10 fewer to 1 fewer) ⊕⊕◯
Interpretation of relative and absolute risks for GLP-1 Agonists compared to sulfonylurea**	GLP-1s reduce all-cause mortality by 33% or 8 fewer events per 1,000 treated	GLP-1s result in no differences in MACE	Insufficient evidence	Insufficient evidence	**GLP-1s probably reduce hospitalization due to CHF by 53% or 13 fewer events per 1,000 treated**	No data	GLP-1s probably result in no differences in SAE	**GLP-1s probably reduce severe hypoglycemia by 51% or 7 fewer events per 1000 treated**
	↓	↔	?	?	↓		↔	↓
GLP-1 Agonists vs. Tirzepatide	K = 1; N = 1,878 *RR 0.25 (0.03, 1.92) 6 fewer (8 fewer to 8 more) ⊕◯◯	NMA RR 1.08 (0.68, 1.73) ⊕◯◯	Tirzepatide is not in network	Tirzepatide is not in network	Tirzepatide is not in network	GLP-1s and tirzepatide are not in network	K = 2; N = 2,143 *RR 0.57 (0.34, 0.96) 24 fewer (37 fewer to 2 fewer) ⊕⊕◯	K = 2; N = 2,143 *RR 0.50 (0.11, 2.23) 4 fewer (7 fewer to 9 more) ⊕◯◯
Interpretation of relative and absolute risks for GLP-1 Agonists compared to tirzepatide**	GLP-1s may result in no difference in all-cause mortality	GLP-1s may result in no difference in MACE	No data	No data	No data	No data	**GLP-1s probably reduce SAE by 43% or 24 fewer events per 1000 treated**	GLP-1s may result in no difference in severe hypoglycemia
	↔	↔					↓	↔

Color key: Favors intervention; Favors comparator; No difference (not colored)

Favors intervention or favors comparator indicates a statistically significant difference between the intervention and comparison or a meaningful difference in effect size (i.e., >25% increase or decrease) with 95% CIs not crossing both lower (0.75) and upper bound (1.25) intervals.

Bold interpretation text indicates statistically significant findings.

Serious adverse events were defined by investigators, varied, and not always fully reported. In general, they included events considered fatal or life threatening, and incorporated events (e.g., stroke, MI) that could also be a clinical benefit (through a reduction) with type 2 diabetes treatment (1). Long-acting insulins and sulfonylureas directly cause hypoglycemia and were used either as a direct comparator or within usual care, which may distort findings.

GRADE certainty of evidence: Insufficient ◯◯◯; Low ⊕◯◯; Moderate ⊕⊕◯; High ⊕⊕⊕

*Estimate from direct comparison because it has a higher certainty of evidence than the network estimate

** Interpretation of findings was done by the Clinical Guidelines Committee; Statistics and GRADE ratings are from the ACP-funded evidence review (1)

Summary of CGC Judgments - GLP-1 Agonists

	GLP-1 AGONISTS VS. DPP-4 INHIBITORS	GLP-1 AGONISTS VS. LONG-ACTING INSULINS	GLP-1 AGONISTS VS. SGLT-2 INHIBITORS	GLP-1 AGONISTS VS. SULFONYLUREAS	GLP-1 AGONISTS VS. TIRZEPATIDE
DESIRABLE EFFECTS	Medium	Medium	Small	Medium	Small
UNDESIRABLE EFFECTS	No clinically meaningful differences	No clinically meaningful differences	Small	No clinically meaningful differences	No clinically meaningful differences
CERTAINTY OF EVIDENCE	Moderate	Moderate	Moderate	Moderate	Low
VALUES	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability
BALANCE OF EFFECTS	Probably favors the intervention	Probably favors the intervention	Probably doesn't favor either the intervention or the comparison	Probably favors the intervention	May favor the intervention
RESOURCES REQUIRED	Modest differences in costs	Modest differences in costs	Modest differences in costs	Large differences in costs	Don't know
COST EFFECTIVENESS	Low-value intervention	No studies	Low-value intervention	Low-value intervention	No studies

Supplement Table 4. Summary of Findings: Long-acting Insulins and Tirzepatide vs. Other Medications

	Number of RCTs; Total Sample Size Risk Ratio (95% Confidence Interval) Absolute Risk Difference per 1,000 Treated Individuals (95% Confidence Interval) Certainty of Evidence							
	All-Cause Mortality	**MACE**	**MI**	**Stroke**	**CHF Hospitalization**	**CKD 3+**	**SAE**	**Severe Hypoglycemia**
Other Head-to-Head Comparisons								
Long-acting Insulins vs. Sulfonylurea	K = 1; N = 2,517 *RR 0.97 (0.64, 1.14) 1 fewer (12 fewer to 16 more) ⊕⊕⊕	K = 1; N = 2,504 *RR 1.09 (0.78, 1.54) 4 more (10 fewer to 26 more) ⊕⊕⊕	Long-acting insulin not in network	Long-acting insulins are not in network	K = 1; N = 2,504 *RR 0.86 (0.51, 1.45) 3 fewer (12 fewer to 11 more) ⊕⊕⊕	Long-acting insulin not in network	NMA RR 1.18 (0.99, 1.41) ⊕◯◯	K = 1; N = 2,517 *RR 0.57 (0.31, 1.04) 10 fewer (15 fewer to 1 more) ⊕⊕◯
Interpretation of relative and absolute risks for long-acting insulins compared to sulfonylurea**	Long-acting insulins result in no differences in all-cause mortality ↔	Long-acting insulins result in no differences in MACE ↔	No data	No data	Long-acting insulins result in no differences in hospitalization due to CHF ↔	No data	Long-acting insulins may result in no differences in SAE ↔	Long-acting insulins probably result in no differences in severe hypoglycemia ↔
Tirzepatide vs. Long-acting insulins	K = 2; N = 3,432 *RR 0.74 (0.45, 1.22) 7 fewer (15 fewer to 6 more) ⊕⊕⊕	K = 1; N = 1,995 *RR 0.76 (0.53, 1.10) 15 fewer (29 fewer to 6 more) ⊕⊕⊕	Long-acting insulins and tirzepatide are not in network	Long-acting insulins and tirzepatide are not in network	Tirzepatide is not in the network	Long-acting insulins and tirzepatide are not in network	K = 2; N = 3,432 *RR 0.80 (0.67, 0.96) 32 fewer (52 fewer to 6 fewer) ⊕◯◯	K = 1; N = 1,437 *RR 0.21 (0.11, 0.38) 57 fewer (64 fewer to 45 fewer) ⊕⊕◯
Interpretation of relative and absolute risks for tirzepatide compared to long-acting insulins **	Tirzepatide results in no differences in all-cause mortality ↔	Tirzepatide results in no differences in MACE ↔	No data	No data	No data	No data	**Tirzepatide may reduce SAEs by 20% or 32 fewer events per 1,000 treated** ↓	**Tirzepatide probably reduces severe hypoglycemia by 79% or 57 fewer events per 1,000 treated** ↓
Tirzepatide vs. Sulfonylurea	◯◯◯	◯◯◯	Tirzepatide is not in network	Tirzepatide is not in network	Tirzepatide is not in network	Tirzepatide is not in network	NMA RR 0.97 (0.78, 1.20) ⊕◯◯	◯◯◯
Interpretation of relative and absolute risks for tirzepatide compared to sulfonylurea**	Insufficient evidence ?	Insufficient evidence ?	No data	No data	No data	No data	Tirzepatide may result in no differences in SAE ↔	Insufficient evidence ?

Color key: Favors intervention; Favors comparator; No difference (not colored)

Favors intervention or favors comparator indicates a statistically significant difference between the intervention and comparison or a meaningful difference in effect size (i.e., >25% increase or decrease) with 95% CIs not crossing both lower (0.75) and upper bound (1.25) intervals.

Bold interpretation text indicates statistically significant findings.

Serious adverse events were defined by investigators, varied, and not always fully reported. In general, they included events considered fatal or life threatening, and incorporated events (e.g., stroke, MI) that could also be a clinical benefit (through a reduction) with type 2 diabetes treatment (1). Long-acting insulins and sulfonylureas directly cause hypoglycemia and were used either as a direct comparator or within usual care, which may distort findings.

GRADE certainty of evidence: Insufficient ◯◯◯; Low ⊕◯◯; Moderate ⊕⊕◯; High ⊕⊕⊕

*Estimate from direct comparison because it has a higher certainty of evidence than the network estimate

** Interpretation of findings was done by the Clinical Guidelines Committee; Statistics and GRADE ratings are from the ACP-funded evidence review (1)

Summary of CGC Judgments - Long-acting Insulins and Tirzepatide

	LONG-ACTING INSULINS VS. SULFONYLUREA	TIRZEPATIDE VS. LONG-ACTING INSULINS	TIRZEPATIDE VS. SULFONYLUREA
DESIRABLE EFFECTS	No clinically meaningful differences	Medium	Don't know
UNDESIRABLE EFFECTS	No clinically meaningful differences	No clinically meaningful differences	Don't know
CERTAINTY OF EVIDENCE	Moderate	Low	Insufficient
VALUES	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability
BALANCE OF EFFECTS	Probably doesn't favor either the intervention or the comparison	May favor the intervention	Don't know
RESOURCES REQUIRED	Large differences in costs	Don't know	Don't know
COST EFFECTIVENESS	Low-value intervention	No studies	No studies

Supplement Table 5. Summary of Findings: SGLT-2 Inhibitors vs. Other Medications

	Number of RCTs; Total Sample Size Risk Ratio (95% Confidence Interval) Absolute Risk Difference per 1,000 Treated Individuals (95% Confidence Interval) Certainty of Evidence							
	All-Cause Mortality	**MACE**	**MI**	**Stroke**	**CHF Hospitalization**	**CKD 3+**	**SAE**	**Severe Hypoglycemia**
SGLT- 2 Inhibitors (Head-to-Head)								
SGLT-2 Inhibitors vs. DPP-4 Inhibitors	K = 5; N=3,878 *RR 0.91 (0.30, 2.78) 0 fewer (1 fewer to 4 more) ⊕◯◯	NMA RR 0.88 (0.80, 0.97) ⊕⊕◯	NMA RR 1.02 (0.85, 1.22) ⊕⊕◯	NMA RR 1.15 (0.87, 1.52) ⊕⊕◯	NMA RR 0.60 (0.48, 0.74) ⊕◯◯	NMA RR 0.62 (0.52, 0.74) ⊕⊕◯	K = 5; N = 3,878 *RR 1.01 (0.76, 1.32) 1 more (13 fewer to 17 more) ⊕⊕⊕	K = 4; N = 3,105 *RR 1. 42 (0.26, 7.59) 0 fewer (1 fewer to 6 more) ⊕◯◯
Interpretation of relative and absolute risks for SGLT-2 inhibitors compared to DPP-4 Inhibitors**	SGLT-2s may result in no differences in all-cause mortality ↔	**SGLT-2s probably reduce MACE by 12%** ↓	SGLT-2s probably result in no differences in MI ↔	SGLT-2s probably result in no differences in stroke ↔	**SGLT-2s may reduce hospitalization due to CHF by 40%** ↓	**SGLT-2s probably reduce progression of CKD by 38%** ↓	SGLT-2s result in no differences in SAEs ↔	SGLT-2s may result in no differences in severe hypoglycemia ↔
SGLT-2 Inhibitors vs. GLP-1 Agonists	NMA RR 0.98 (0.89, 1.08) ⊕⊕◯	NMA RR 0.99 (0.90, 1.09) ⊕⊕◯	NMA RR 1.01 (0.86, 1.18) ⊕⊕◯	NMA RR 1.30 (1.05, 1.61) ⊕⊕◯	NMA RR 0.69 (0.56, 0.86) ⊕⊕◯	GLP-1 not in network	K = 2; N = 1,249 *RR 1.08 (0.83, 1.41) 5 more (10 fewer to 24 more) ⊕⊕◯	K = 3; N = 2,068 *RR 1.00 (0.47, 2.14) 0 fewer (7 fewer to 14 more) ⊕⊕◯
Interpretation of relative and absolute risks for SGLT-2 Inhibitors compared to GLP-1 Agonists**	SGLT-2s probably result in no differences in all-cause mortality ↔	SGLT-2s probably result in no differences in MACE ↔	SGLT-2s probably result in no differences in MI ↔	**SGLT-2s probably increase stroke by 30%** ↑	**SGLT-2s probably reduce hospitalization due to CHF by 31%** ↓	No data	SGLT-2s probably result in no differences in SAEs ↔	SGLT-2s probably result in no differences in severe hypoglycemia ↔
SGLT-2 Inhibitors vs. Long-acting insulins	NMA RR 0.70 (0.51, 0.98) ⊕◯◯	NMA RR 0.81 (0.61, 1.09) ⊕◯◯	Long-acting insulins are not in network	Long-acting insulins are not in network	NMA RR 0.64 (0.39, 1.04) ⊕◯◯	Long-acting insulins are not in network	NMA RR 0.79 (0.67, 0.94) ⊕◯◯	NMA RR 0.22 (0.15, 0.32) ⊕◯◯
Interpretation of relative and absolute risks for SGLT-2 Inhibitors compared to long-acting insulins**	**SGLT-2s may reduce all-cause mortality by 30%** ↓	SGLT-2s may result in no differences in MACE ↔	No data	No data	**SGLT-2s may reduce hospitalization due to CHF by 36%** ↓	No data	**SGLT-2s may reduce SAEs by 21%** ↓	**SGLT-2s may reduce severe hypoglycemia by 78%.** ↓
SGLT- 2 Inhibitors vs. Sulfonylurea	K = 4; N = 5,134 *RR 1.09 (0.55, 2.20)	K = 2; N = 2,995 *RR 0.57 (0.36, 0.91)			K = 1; N = 625 *RR 0.33 (0.01, 8.13)	Sulfonylurea is not in network	K =5; N = 5,560 *RR 0.99 (0.87, 1.14)	K = 5; N = 5,744 *RR 0.10 (0.07, 0.15)

	1 more (3 fewer to 9 more) ⊕⊕◯	14 fewer (21 fewer to 3 fewer) ⊕⊕⊕	◯◯◯	◯◯◯	2 fewer (3 fewer to 23 more) ⊕◯◯		0 fewer (20 fewer to 21 more) ⊕⊕⊕	83 fewer (86 fewer to 79 fewer) ⊕⊕⊕
Interpretation of relative and absolute risks for SGLT-2 Inhibitors compared to sulfonylurea**	SGLT-2s probably result in no differences in all-cause mortality	**SGLT -2s reduce MACE by 43% or 14 fewer events per 1000 treated**	Insufficient evidence	Insufficient evidence	SGLT -2s may result in no differences in hospitalization due to CHF	No data	SGLT- 2s result in no differences in SAE	**SGLT- 2s reduce severe hypoglycemia by 90% or 83 fewer events per 1000 treated**
	↔	↓	?	?	↔		↔	↓
SGLT- 2 Inhibitors vs. Tirzepatide	◯◯◯	◯◯◯	Tirzepatide is not in network	Tirzepatide is not in network	Tirzepatide is not in network	Tirzepatide is not in network	NMA RR 0.96 (0.78, 1.19) ⊕◯◯	NMA RR 0.76 (0.50, 1.17) ⊕◯◯
Interpretation of relative and absolute risks for SGLT-2 Inhibitors compared to tirzepatide**	Insufficient evidence	Insufficient evidence	No data	No data	No data	No data	SGLT- 2s may result in no difference in SAE	SGLT- 2s may result in no difference in severe hypoglycemia
	?	?					↔	↔

Color key: Favors intervention; Favors comparator; No difference (not colored)

Favors intervention or favors comparator indicates a statistically significant difference between the intervention and comparison or a meaningful difference in effect size (i.e., >25% increase or decrease) with 95% CIs not crossing both lower (0.75) and upper bound (1.25) intervals.

Bold interpretation text indicates statistically significant findings.

Serious adverse events were defined by investigators, varied, and not always fully reported. In general, they included events considered fatal or life threatening, and incorporated events (e.g., stroke, MI) that could also be a clinical benefit (through a reduction) with type 2 diabetes treatment (1). Long-acting insulins and sulfonylureas directly cause hypoglycemia and were used either as a direct comparator or within usual care, which may distort findings.

GRADE certainty of evidence: Insufficient ◯◯◯; Low ⊕◯◯; Moderate ⊕⊕◯; High ⊕⊕⊕

*Estimate from direct comparison because it has a higher certainty of evidence than the network estimate

** Interpretation of findings was done by the Clinical Guidelines Committee; Statistics and GRADE ratings are from the ACP-funded evidence review (1)

Summary of CGC Judgments – SGLT-2 Inhibitors

	SGLT-2 INHIBITORS VS. DPP-4 INHIBITORS	SGLT-2 INHIBITORS VS. GLP-1 AGONISTS	SGLT-2 INHIBITORS VS. LONG-ACTING INSULINS	SGLT-2 INHIBITORS VS. SULFONYLUREAS	SGLT-2 INHIBITORS VS. TIRZEPATIDE
DESIRABLE EFFECTS	Medium	Small	Medium	Medium	Don't know
UNDESIRABLE EFFECTS	No clinically meaningful differences	Small	No clinically meaningful differences	No clinically meaningful differences	No clinically meaningful differences
CERTAINTY OF EVIDENCE	Low	Moderate	Low	Moderate	Insufficient
VALUES	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability
BALANCE OF EFFECTS	May favor the intervention	Probably doesn't favor either the intervention or the comparison	May favor the intervention	Probably favors the intervention	Don't know
RESOURCES REQUIRED	Negligible differences in costs and savings	Modest differences in savings	Negligible differences in costs and savings	Modest differences in costs:	Don't know
COST EFFECTIVENESS	No studies	No studies	No studies	No studies	No studies

Values and Preferences

Systematic Review and CGC Public Panel Survey: Summary of Findings

The CER conducted a systematic review on patients' values and preferences and found 3 eligible reviews (1). One review concluded low or very low CoE according to GRADE criteria mostly due to high risk of bias in the majority of included studies (Supplement Table 6)(2). The other 2 reviews reported low RoB in the included studies (3, 4). However, the Purnell (3) and Gonzalez-Gonzalez (2) reviews both cite a concern with the number of industry funded trials.

All reviews identified glycemic control, weight loss, route and frequency of administration, hypoglycemic episodes, and gastrointestinal events as attributes patients take into consideration when choosing medications. Two reviews also reported that cardiovascular risk reduction (2, 4) was important for patients. One review suggested that the cost of medicines (as additional payment per month) was ranked as important by 30% of patients (4).

A Survey of the CGC Public Panel

Responses from the Public Panel (N = 2/6) about benefits and harms of the different pharmacological treatments indicated a preference for use of SGLT-2 inhibitors and GLP-1 agonists, and uncertainty in use of DPP-4 inhibitors. Responses were mixed for tirzepatide and long-acting insulin; preference to use/suggest use was driven by benefits demonstrated in comparative effectiveness to other pharmacological treatments. Qualitative comments acknowledged the importance of additional considerations for decision-making such as the route and frequency of administration and cost.

Supplement Table 6. Values and Preferences Regarding Treatments in Adults with Type 2 Diabetes (1)

Author Name, Year Number of studies (k)	Primary Aim	Authors Conclusions
Gonzalez-Gonzalez, 2021(2) K=17	To assess values, preferences, and burden of treatment that patients with type 2 diabetes consider when initiating glucagon-like peptide-1 receptor agonists (GLP-1 agonists) or sodium-glucose contransporter-2 inhibitors (SGLT-2 inhibitors) compared with other glucose-lowering options.	GLP-1 agonists Cardiovascular risk reduction, glucose lowering potential, and simple administration regimens (e.g. once weekly alternatives over daily injections) were the most preferred. No evidence on preferences regarding initiation of SGLT-2 inhibitors.
Toroski, 2019 (4) K = 17	To assess patients' preferences about antidiabetic medicines and extract attributes of anti-diabetic medicines and their relative importance.	Changes of blood glucose and HbA1c level (100% of people who considered attributes to be important significantly from their perspective), hypoglycemia events (100%), weight changes (84%), cost of medicines (as additional payment per month,31%), mode of administration (59%), dosage frequency (79%),

		gastrointestinal complications (nausea, vomiting, diarrhea, 78%), risk of serious heart attack or stroke (68%) were the most preferred.
Purnell, 2014 (3) K = 10	To identify and analyze patient preferences in patients with type 2 diabetes not on insulin.	Weigh loss/control and glycemic control as key attributes of diabetes treatment that drive patient preferences when these factors were compared with treatment burden and side effects. Gastrointestinal effects were ranked as more important than hypoglycemia by patients within the included studies. Evidence on patient preferences related to other treatment-related attributes of risk and burden was sparse.

Supplement Table 7. Average Annual Medicare Spending Per Beneficiary on Medications Indicated as an Add-On to Diet and Exercise to Improve Glycemic Control in Adults with Type 2 Diabetes (5)

Drug class	Lowest (≤33rd Percentile) in Average Spending Per Beneficiary in CY 2021†		Medium (>33 to ≤66th Percentile) in Average Spending Per Beneficiary in CY 2021†		Highest (>66th Percentile) in Average Spending Per Beneficiary in CY 2021†	
DPP-4 inhibitors	Alogliptin benzoate (Alogliptin)	$878	alogliptin benzoate (Nesina)	$1,634	saxagliptin HCl (Onglyza)	$4,081
					linagliptin (Tradjenta)	$4,136
					sitagliptin phosphate (Januvia)	$4,344
DPP-4 inhibitors combined with metformin	alogliptin benz/metformin HCl (Alogliptin-Metformin)	$709	alogliptin benz/metformin HCl (Kazano)	$2,501	sitagliptin phos/metformin HCl (Janumet XR	$3,922
			linagliptin/metformin HCl (Jentadueto XR)	$3,773	saxagliptin HCl/metformin HCl (Kombiglyze XR)	$4,129
					linagliptin/metformin HCl (Jentadueto)	$4,182
					Sitagliptin Phos/Metformin HCl (Janumet)	$4,232
DPP-4 inhibitors combined with SGLT-2 Inhibitors			ertugliflozin/sitagliptin (Steglujan)	$3,187	empagliflozin/linagliptin (Glyxambi)	$4,388
			dapagliflozin/saxagliptin HCl (Qtern)	$3,823		
DPP-4 inhibitors combined with thiazolidinedione-type	alogliptin benz/pioglitazone (Alogliptin-Pioglitazone)	$1,291	alogliptin benz/pioglitazone (Oseni)	$3,465		
GLP-1 agonists			exenatide microspheres (Bydureon Pen)	$2,313	lixisenatide (Adlyxin)	$3,971
			liraglutide (Victoza 2-Pak)	$3,656	semaglutide (Rybelsus)	$4,200
					semaglutide (Ozempic)	$5,716

					exenatide microspheres (Bydureon BCise)	$5,719
					exenatide (Byetta)	$6,047
					dulaglutide (Trulicity)	$7,083
					liraglutide (Victoza 3-Pak)	$7,093
GLP-1 agonists combined with insulin					insulin glargine/lixisenatide (Soliqua 100-33)	$4,547
					insulin degludec/liraglutide (Xultophy 100-3.6)	$6,603
SGLT-2 inhibitors	Ertugliflozin Pidolate (Steglatro)	$1,480	Dapagliflozin Propanediol (Farxiga)	$3,686	Canagliflozin (Invokana)	$4,177
					Empagliflozin (Jardiance)	$4,224
SGLT-2 inhibitors combined with DPP-4 inhibitor and metformin			Empagliflozin/Linagliptin/Metformin (Trijardy XR)	$3,059		
SGLT-2 inhibitors combined with metformin	Ertugliflozin/Metformin (Segluromet)	$1,332	Canagliflozin/Metformin HCl (Invokamet XR)	$3,517		
			Dapagliflozin/Metformin HCl (Xigduo XR)	$3,914		
			Canagliflozin/Metformin HCl (Invokamet)	$3,956		
			Empagliflozin/Metformin HCl (Synjardy)	$4,001		
			Empagliflozin/Metformin HCl (Synjardy XR)	$4,018		

Abbreviations. DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SGLT-2: sodium-glucose co-transporter-2; CY: calendar year; benz: benzoate; HCL: hydrochloride; phos: phosphate

Note. When available, brand names are listed in () below generic names of drugs.

†Total spending in CY 2021 divided by total beneficiaries in CY 2021 for each drug regardless of individual patient indications. The Medicare spending on tirzepatide was not available for 2021.The column is sorted from the lowest to the highest under each group.

Cost data in the 33rd percentile or lower ($0 to 1,526) is highlighted in green; above the 33rd percentile to the 66th percentile (>$1,526 to $3,918) is highlighted in orange; and data above the 66th percentiles (>$3,918) is highlighted in red

Supplement Table 7 (cont.). Average Annual Medicare Spending Per Beneficiary on Medications Indicated as an Adjunct to Diet and Exercise to Improve Glycemic Control in Adults with Type 2 Diabetes (5)

Drug class	Lowest (≤33rd Percentile) in Average Spending Per Beneficiary in CY 2021†		Medium (>33 to ≤66th Percentile) in Average Spending Per Beneficiary in CY 2021†		Highest (>66th Percentile) in Average Spending Per Beneficiary in CY 2021†	
Sulfonylureas	Glipizide (Glipizide)	$34	Glyburide, Micronized (Glynase)	$1,812.01		
	Glipizide (Glipizide XL)	$47				
	Glimepiride (Glimepiride)	$50				
	Glipizide (Glipizide ER)	$79				
	Glyburide (Glyburide)	$80				
	Glyburide, Micronized (Glyburide Micronized)	$80				
	Glipizide (Glucotrol)	$752				
	Glipizide (Glucotrol XL)	$1,024				
	Glimepiride (Amaryl)	$1,343				
Sulfonylureas combined with metformin	Glyburide/Metformin HCl (Glyburide-Metformin HCl)	$77				
	Glipizide/Metformin HCl (Glipizide-Metformin)	$256				
Metformin	Metformin HCl (Metformin HCl)	$31	Metformin HCl (Metformin ER Osmotic)	$1,640	Metformin HCl (Metformin ER Gastric)	$6,773
	Metformin HCl (Metformin HCl ER)	$41	Metformin HCl (Riomet)	$1,689		

Abbreviations. DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SGLT-2: sodium-glucose co-transporter-2; CY: calendar year; benz: benzoate; HCL: hydrochloride; phos: phosphate

Note. When available, brand names are listed in () below generic names of drugs.

†Total spending in CY 2021 divided by total beneficiaries in CY 2021 for each drug regardless of individual patient indications. The column is sorted from the lowest to the highest under each group. Glumetza was excluded from percentile calculations due to being an outlier (i.e., $37,463).

Supplement Table 8. Average Annual Medicare Spending on Long-acting Insulins Per Beneficiary (5)

	Lowest (≤33rd Percentile) in Average Spending Per Beneficiary in CY 2021†		Medium (>33 to ≤66th Percentile) in Average Spending Per Beneficiary in CY 2021†		Highest (>66th Percentile) in Average Spending Per Beneficiary in CY 2021†	
Long-acting Insulins	Insulin Glargine-Yfgn* (Insulin Glargine-Yfgn)	$107	Insulin Lispro (Humalog Junior Kwikpen)	$1,672	Insulin Aspart (Niacinamide) (Fiasp)	$4,165
	Insulin Glargine, Hum. Rec. Anlog (Semglee Pen)	$245	Insulin Lispro Protamine/Lispro (Insulin Lispro Protamine Mix)	$1,828	Insulin Glargine, Hum. Rec. Anlog (Toujeo Max Solostar)	$4,499
	Insulin Glargine-Yfgn* (Semglee (Yfgn) Pen)	$259	Insulin Glargine, Hum. Rec. Anlog (Basaglar Kwikpen U-100)	$1,839	Insulin Aspart Prot/Insulin Asp (Novolog Mix 70-30)	$4,615
	Insulin Glargine, Hum. Rec. Anlog (Semglee)	$284	Insulin Lispro-Aabc* (Lyumjev Kwikpen U-100)	$2,173	Insulin Lispro Protamine/Lispro (Humalog Mix 75-25)	$4,684
	Insulin Lispro (Admelog)	$311	Insulin Aspart (Niacinamide) (Fiasp Penfill)	$2,238	Insulin Lispro (Humalog Kwikpen U-200)	$5,211
	Insulin Glargine-Yfgn* (Semglee (Yfgn))	$368	Insulin Aspart (Novolog Penfill)	$2,259	Insulin Lispro Protamine/Lispro (Humalog Mix 75-25 Kwikpen)	$5,246
	Insulin Lispro (Admelog Solostar)	$435	Insulin Degludec (Tresiba)	$2,579	Insulin Degludec (Tresiba Flextouch U-200)	$5,305
	Insulin Lispro (Insulin Lispro Junior Kwikpen)	$592	Insulin Lispro (Humalog)	$2,597	Insulin Lispro Protamine/Lispro (Humalog Mix 50-50)	$5,327
	Insulin Aspart (Insulin Aspart Penfill)	$653	Insulin Glargine, Hum. Rec. Anlog (Lantus Solostar)	$2,685	Insulin Aspart Prot/Insulin Asp (Novolog Mix 70-30 Flexpen)	$5,409
	Insulin Aspart (Insulin Aspart)	$688	Insulin Glargine, Hum. Rec. Anlog (Lantus)	$2,762	Insulin Lispro Protamine/Lispro (Humalog Mix 50-50 Kwikpen)	$5,618
	Insulin Aspart (Insulin Aspart Flexpen)	$744	Insulin Degludec (Tresiba Flextouch U-100)	$2,859		
	Insulin Lispro (Insulin Lispro)	$991	Insulin Lispro (Humalog Kwikpen U-100)	$2,875		
	Insulin Lispro (Insulin Lispro Kwikpen U-100)	$1,042	Insulin Lispro-Aabc (Lyumjev)	$2,908		
	Insulin Aspart Prot/Insulin Asp (Insulin Aspart Prot Mix 70-30)	$1,320	Insulin Aspart (Niacinamide) (Fiasp Flextouch)	$2,979		
			Insulin Aspart (Novolog)	$3,135		

		Insulin Detemir (Levemir)	$3,162	
		Insulin Aspart (Novolog Flexpen)	$3,206	
		Insulin Glargine, Hum.Rec.Anlog (Toujeo Solostar)	$3,423	
		Insulin Detemir (Levemir Flextouch)	$3,480	
		Insulin Lispro-Aabc (Lyumjev Kwikpen U-200)	$3,903	

Abbreviations. Hum. Rec. Anlog: human recombinant analogue *- biosimilars; When available, brand names are in () below generic names †Total spending in CY 2021 divided by total beneficiaries in CY 2021 for each drug. The column is sorted from the lowest to the highest national spending

Cost Effectiveness

Supplement Table 9. Summary of Findings from the Systematic Review of Cost-effectiveness Analyses of Newer Pharmacological Treatments in Adults with Type 2 Diabetes (6)

Authors	Intervention	Comparator	Author Reported Cost per QALY Gained adjusted to 2022 US Dollars	Certainty of evidence	Value Interpretation*
GLP-1 agonists vs. background therapy and GLP-1 agonists vs. Other medication					
Choi, 2022(7)	First line treatment with GLP-1 agonists	Metformin	Oral GLP-1 agonists vs. Metformin = $823,000 per QALY Oral GLP-1 agonists vs. SGLT-2 inhibitor had an ICER of $1,024,000 per QALY	High	Injectable GLP-1 agonists cost more and shorten quality-adjusted life expectancy compared to metformin. Oral GLP-1 agonists are of low value compared with metformin or SGLT-2 inhibitor as first line treatments.
Abramson, et al 2019 (8)	Semaglutide 40 mg oral daily or Semaglutide 1 mg subcutaneous weekly	Background therapy	Daily Oral capsule vs. background Male = $92,000 Female = $105,000 Weekly Subcutaneous vs background: Male = $99,000 Female: = $148,000	Moderate	Semaglutide (GLP-1 agonists) (oral or injectable) is probably of intermediate value vs. background therapy
Guzauskas, et al 2020 (9)	Oral semaglutide (14 mg daily) + background therapy	Background therapy	Oral semaglutide vs. background therapy = $122,000 (< 5% probability < $50,000 and 21% probability > $156,000)	Low	Semaglutide (GLP-1 agonist) may be of intermediate value vs. background therapy
		Sitagliptin + background therapy (100 mg daily)	Oral semaglutide vs. sitagliptin = $151,000 (<5% probability < $50,000)	Low	Oral semaglutide (GLP-1 agonist) may be of low value vs. sitagliptin (DPP-4 inhibitor)
		Empagliflozin (10 mg or 25 mg) +	Oral semaglutide vs. empagliflozin = $477,000 (8%	Low	Oral semaglutide (GLP-1 agonist) may be of low value vs

		background therapy	probability <$156,000)		empagliflozin (SGLT-2 inhibitor)
		Injectable liraglutide + background therapy (1.8 mg daily)	Oral semaglutide vs. liraglutide = $42,000 (98% probability <$156,000)	Low	Oral semaglutide (GLP-1 agonist) may be of high value vs liraglutide (GLP-1 agonist)
Sinha, 2010(10)	GLP-1 agonist (exenatide) **vs**. Sulfonylureas (glyburide) *added to* Metformin	Metformin	Exenatide vs. Glyburide = $353,522.78	Insufficient	Unable to assess value of GLP-1 agonist compared with sulfonylureas when added to metformin (insufficient evidence)
Sinha, 2010(10)	GLP-1 agonist (exenatide vs. DPP-4 inhibitor(sitagliptin) added to Metformin	Metformin	Sitagliptin vs. Glyburide = $214,915.90 Exenatide vs. Sitagliptin = cost more and provided fewer QALYs	Low	GLP-1 agonist may be of low value compared with DPP-4 inhibitor when added to metformin.
Tirzepatide vs. Background and Tirzepatide vs. Other medication					
Lin, et al 2021 (11)	Tirzepatide + background therapy	Background therapy	Tirzepatide vs. Background therapy = $59,000 (95% CI $11,000 - $101,000)	Insufficient	Tirzepatide is of uncertain value vs. background therapy
		Injectable semaglutide plus background therapy	Tirzepatide vs Injectable semaglutide: less expensive, more effective (95% C.I - $1.5 million to +$1.4 million)	Insufficient	Tirzepatide is of uncertain value vs. injectable semaglutide (GLP-1 agonist) plus background therapy
		Empagliflozin plus background therapy	Tirzepatide vs. Empagliflozin = $103,000 (95% C.I. -$56,000 to $338,000)	Insufficient	Tirzepatide is of uncertain value vs. empagliflozin (SGLT-2 inhibitor) plus background therapy
SGLT-2 inhibitors vs. background therapy					
Choi, 2022(7)	First line treatment with SGLT-2 inhibitors	Metformin	SGLT-2 inhibitor vs. metformin = $478,000 per QALY	High	SGLT-2 inhibitors are of low value compared with metformin as a first line treatment.
Nguyen, et al 2016 (12)	Empagliflozin (10 mg or 25 mg)	Standard of care	Empagliflozin vs standard of care = $86,000 (96% probability <$113,000)	Low	Empagliflozin (SGLT-2 inhibitor) may be of intermediate value vs. usual care/background therapy
Insulin degludec vs. insulin glargine					

Tice, et al 2014 (13)	Insulin degludec	Insulin glargine U100	Insulin degludec vs glargine Basal insulin only = $406,000* Basal plus bolus insulin = $192,000	Moderate	Insulin degludec is probably of low value vs. insulin glargine (with or without bolus insulin)
Second-line treatment added to metformin					
ICER - CEPAC December 2014 (14)	Sulfonylureas (glipizide/glyburide), DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin), GLP-1 agonists (exenatide, liraglutide, dulaglutide, albiglutide) long-acting insulin analogs, and NPH insulin.	Metformin, sulfonylureas	GLP-1 agonist + metformin vs sulfonylurea = $807,000	Low	GLP-1 agonist + metformin may be of low value vs. sulfonylureas
			DPP-4 vs sulfonylurea = more expensive, less effective (ICER per QALY not reported)	Low	DPP-4 may be more expensive and less effective vs. sulfonylureas.
			Insulin analog vs sulfonylurea = $1,194,000	Low	Insulin analogs may be of low value vs. to sulfonylureas
Third-line treatment added to metformin + sulfonylurea					
ICER - CEPAC December 2014 (14)	DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin), GLP-1 agonists (exenatide, liraglutide, dulaglutide, albiglutide), long-acting insulin analogs, and NPH insulin.	Metformin + sulfonylurea	Third-line treatment added to metformin + sulfonylurea: GLP-1 agonist vs NPH insulin = $2,072,000	Low	Third-line treatment added to metformin + sulfonylurea: GLP-1 agonist may be of low value compared to NPH insulin.
			DPP-4 vs. NPH insulin = more expensive, less effective	Low	DPP-4 may be more expensive and less effective compared to NPH insulin
			Insulin analog vs. NPH insulin = more expensive, equally effective	Low	Insulin analog may be similarly effective but more expensive compared to NPH insulin

*Economic value thresholds based on ACP CGC consensus around willingness to pay thresholds:

- **High value**: Cost-saving or < $50k ICER per QALY gained
- **Intermediate value**: $50k to $150K ICER per QALY gained
- **Low value**: >$150k ICER per QALY gained
- **Uncertain value**: The evidence is insufficient to draw a conclusion about clinical effectiveness and the cost-effectiveness of intervention(s)

References

1. Drake T, Landsteiner, A., Langsetmo, L., MacDonald, R., Anthony, M., Kalinowski, C., Ullman, K., Billington, C.J., Kaka, A., Sultan, S., Wilt, T.J. Newer Treatments for Adults with Type 2 Diabetes Mellitus: A Systematic Review and Network Meta-Analysis for the American College of Physicians Clinical Guidelines Committee. Ann Intern Med. 2024;Pending.
2. González-González JG, Díaz González-Colmenero A, Millán-Alanís JM, Lytvyn L, Solis RC, Mustafa RA, et al. Values, preferences and burden of treatment for the initiation of GLP-1 receptor agonists and SGLT-2 inhibitors in adult patients with type 2 diabetes: a systematic review. BMJ Open. 2021;11(7):e049130.
3. Purnell TS, Joy S, Little E, Bridges JFP, Maruthur N**.** Patient Preferences for Noninsulin Diabetes Medications: A Systematic Review. Diabetes Care. 2014;37:2055-62.
4. Toroski M, Kebriaeezadeh A, Esteghamati A, Karyani AK, Abbasian H, Nikfar S**.** Patient and physician preferences for type 2 diabetes medications: a systematic review. Journal of Diabetes & Metablic Disorders. 2019;18:643-56.
5. U.S. Centers for Medicare & Medicaid Services. Medicare Part D Drug Spending Dashboard & Data. 2021. Accessed at https://data.cms.gov/summary-statistics-on-use-and-payments/medicare-medicaid-spending-by-drug/medicare-part-d-spending-by-drug on February 2024.
6. Schousboe JT, Landsteiner AD, T. , Sultan SL, L. Kaka, A. , Anthony MB, C. Kalinowski, C. Ullman, K. , Wilt T**.** Cost-Effectiveness of Newer Treatments in Adults with Type 2 Diabetes: A Systematic Review of Cost-effectiveness Studies for a Clinical Guideline of the American College of Physicians. Ann Intern Med. 2024;Pending.
7. Choi JG, Winn AN, Skandari R, Franco MI, Staab EM, Alexander J, et al. First-Line Therapy for Type 2 Diabetes With Sodium-Glucose Cotransporter-2 Inhibitors and Glucagon-Like Peptide-1 Receptor Agonists A Cost-Effectiveness Study. Annals of Internal Medicine. 2022;175(10).
8. Abramson A, Halperin F, Kim J, Traverso G**.** Quantifying the Value of Orally Delivered Biologic Therapies: A Cost-Effectiveness Analysis of Oral Semaglutide. J Pharm Sci. 2019;108(9):3138-45.
9. Guzauskas GF, Rind DM, Fazioli K, Chapman RH, Pearson SD, Hansen RN**.** Cost-effectiveness of oral semaglutide added to current antihyperglycemic treatment for type 2 diabetes. J Manag Care Spec Pharm. 2021;27(4):455-68.
10. Sinha A, Rajan M, Hoerger T, Pogach L**.** Costs and consequences associated with newer medications for glycemic control in type 2 diabetes. Diabetes Care. 2010;33(4):695-700.
11. Lin G, Brouwer E, Nikitin D, Moradi A, Chen Y, Herron-Smith S, et al. Tirzepatide for type 2 diabetes: Final report. 2022. Accessed at https://icer.org/wp-content/uploads/2021/06/ICER_Type2Diabetes_FinalReport_02152022.pdf on February 2024.
12. Nguyen E, Coleman CI, Nair S, Weeda ER**.** Cost-utility of empagliflozin in patients with type 2 diabetes at high cardiovascular risk. J Diabetes Complications. 2018;32(2):210-5.
13. Tice J, Ollendorf D, Chapman R, Shore K, Weissberg J, Pearson S**.** Insulin Degludec (Tresiba®, Novo Nordisk A/S) for the Treatment of Diabetes: Effectiveness, Value, and Value-Based Price Benchmarks. 2016. Accessed at https://icer.org/wp-content/uploads/2020/10/Diabetes_Draft_Report_122115-1.pdf on February 2024.
14. The New England Comparative Effectiveness Public Advisory Council. Controversies in the management of patients with type 2 diabetes. 2014. Accessed at https://icer.org/wp-content/uploads/2020/09/CEPAC-T2D-Final-Report-December-22.pdf on February 2024.